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## A Study of the Transmission of Sensory Information in the Cat Spinal Cord

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A STUDY OF THE TRANSMISSION OF SENSORY INFORMATION IN  
THE CAT SPINAL CORD

A thesis submitted to the Faculty of The Rockefeller Institute  
in partial fulfillment of the requirements  
for the degree of Doctor of Philosophy

by  
Paul R. Burgess

25 June 1965

The Rockefeller Institute

New York, New York



## PREFACE

Many have helped in carrying out the work which is presented in this thesis. I would like to thank especially Dr. Victor Wilson for his insightful guidance as research advisor, Dr. David Lange and Dr. Frederick Dodge for help in computer programming, Dr. H.K. Hartline for the use of computer facilities, Dr. Robert Schoenfeld and Mr. Lawrence Eisenberg for help with electronic problems, and my wife Jane for much help with the manuscript and general encouragement.

I would also like to thank The Rockefeller Institute for providing the opportunity, intellectual atmosphere, and technical facilities which made this research possible.

ABSTRACT

With the hope of elucidating neurophysiological mechanisms involved in cutaneous modality discrimination, a comparison was made between activity recorded from single fibers in the dorsal columns and lateral funiculus of the cat spinal cord. Information obtained from human subjects with spinal lesions had indicated that the main impairment following dorsal column transection was one of tactile discrimination and position sense, whereas the major impairments following lateral column lesions involved thermal sensations and pain. It was considered of interest to determine whether individual fibers in these regions were responsive to more than one kind of cutaneous stimulation (touch and cooling for example) or whether individual fibers were specific, responding to only one kind of stimulation. If single fibers were found to be polymodal, the possibility had to be considered that stimuli related to a particular modality might set up a characteristic temporal pattern of discharge which would differ in a reproducible fashion from patterns elicited by stimuli related to other modalities. In this way information regarding the kind of cutaneous stimulation which had occurred might be preserved in a polymodal pathway.

It was found that all fibers in the dorsal columns which could be influenced from the skin were driven to highest frequencies by mechanical stimulation. Rapidly moving stimulators were the most effective. Mechanical or thermal stimuli vigorous enough to damage the skin caused inactivation of cutaneous dorsal column units. Rapidly adapting units were the most frequently encountered in the dorsal columns, and these showed no response to thermal stimuli. More slowly adapting dorsal column units responded weakly to rapid cooling, the activity during this response being more regular than that typically seen during mechanically evoked activity of equivalent frequency. The possibility therefore exists that slowly adapting dorsal column units convey information concerning both mechanical events and cooling, but the fact that the highest frequencies which occur in response to rapid cooling are never more than 10% of the maximal frequency occurring in response to appropriate mechanical stimulation suggests that the cooling response may be of minor importance.

All the lateral funicular units studied in the present experiments were polymodal, responding to mechanical stimulation, noxious heating and rapid cooling. Vigorous and damaging thermal or mechanical stimuli did not inactivate these units. No characteristically different patterns of activity in response to particular kinds of effective stimuli were seen in the population as a whole. The most striking differences in temporal patterning seen were between different units, and seemed to be characteristic of the unit and not of the kind of stimulation used to activate it.

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# A Study of the Transmission of Sensory Information in the Cat Spinal Cord

## Introduction

There is general agreement that in man four main types of modalities of sensation can be aroused by stimulation of the skin: warmth, cold, pain, and touch. By warmth and cold are meant those sensations which are evoked by small or moderate increases or decreases in skin temperature (changes of  $0.1^{\circ}\text{C}$  are sufficient); pain is generally associated with stimuli, whatever their nature, which cause tissue damage; and cutaneous touch provides information about mechanical events at the surface of the body. It is clear that animals other than man also receive information about temperature changes, damage, and mechanical events involving the body surface. A question which arises concerns the way in which an animal distinguishes stimuli of different modalities, and the extent to which the pathways which subserve different modalities are anatomically separate. This must be known before an investigation of neural activity related to any one modality can be properly undertaken. Two alternative mechanisms for information transfer can be considered: 1. There exist separate receptors, pathways, and central connections for activity related to each of the sensory modalities. 2. At some point prior to the highest centers there is convergence of activity related to different modalities onto the same neuron, the information regarding the nature of the stimulus then being conveyed by some characteristic pattern of discharge. This convergence could occur at the level of the primary receptors in the skin, or at any other synaptic relay before the stimulus is perceived. Whatever the mechanism, the neural systems which subserve each modality must be organized so that the organism can appreciate the strength of the stimulus. In the experiments to be described below the method of single unit recording has been used in an attempt to determine how information is transferred in neural pathways influenced by skin stimulation. While recording from a single cell it is possible to subject the skin to a variety of stimuli, and in this way to test directly whether stimuli related to different modalities converge onto a single neural element. This method suffers from the limitation that nerve cells are examined individually. Only by artificially synthesizing the activity of many individual units at a later time is it possible to obtain any impression of the behavior of the total population which is responding. It is presumably this population response which determines the actual information transferred.

The spinal cord may offer a favorable location for a study of the ways in which modality discrimination is achieved. There is evidence, to be considered in detail later, for an anatomical separation of pathways within the cord, such that information needed for fine tactile discriminations is conveyed in one region, and information required for the experience of pain and thermal sensations in another. By recording the activity of single nerve fibers which are influenced from the skin and which lie in these different parts of the spinal cord it should be possible to obtain information about the mechanisms associated with these sensations. An additional reason for recording at the spinal level, rather than more centrally or more peripherally in the nervous system, is that sensory mechanisms at this level have been relatively little studied. An interesting question in neurophysiology has to do with the way in which information is processed by the nervous system. In order to understand how and to what extent processing occurs it is necessary to characterize both the activity that enters and the activity that leaves that portion of the nervous system being considered. Although a number of studies have been undertaken to analyse the properties of primary afferent fibers terminating in the skin, and to investigate the activity of the cells responding to cutaneous stimuli in the brain stem and cerebral cortex, little is known about the connecting link between the periphery and the brain - the spinal cord. Finally, it was thought that a study of the responses of units in the spinal cord to quantitative and defined stimuli might establish a basis for extending analysis to more rostral parts of the central nervous system. In the introductory discussion which follows there will first be a consideration of some aspects of the anatomy of the somatosensory system, in particular the structure of receptors in the skin, and the arrangement of fiber systems in the spinal cord, followed by a consideration of electrophysiological studies which provide information concerning the extent to which individual neurons respond specifically to different cutaneous stimuli.

## I. Anatomical Considerations

### A. Structure of receptors in the skin

It has long been known that in man it is easier to evoke a particular sensation from some points on the skin surface than from others, and that low threshold points for stimuli of one modality are distributed independently of those for other modalities. A question of interest is whether there are anatomically distinct receptors associated with these low threshold sites, with each cutaneous modality possessing a receptor which differs in gross structural

appearance from receptors associated with other modalities. Demonstration of such differences would provide support for the concept that there are receptors which respond specifically to stimuli of a particular modality. Perhaps the most direct way to approach this question is to locate a low threshold point to a particular stimulus, excise the underlying skin, and examine it under the microscope after suitable staining. This technique has been applied to man by a number of investigators, beginning with Donaldson in 1885 (Dallenbach 1927, Pendleton 1928, Wollard 1935, Gilmer and Haythorn 1941. See Dallenbach 1929 for references to early literature). Low threshold sites for warmth and cold have been examined most often, and in almost all cases the excised skin has been taken from hairy regions of the body. (Any portion of the skin which contains hair follicles is called hairy skin. Only a few relatively small areas do not possess hair follicles; examples are the palms of the hands, soles of the feet, conjunctiva, and various mucocutaneous junctions such as the lips and anal region. The skin covering these hairless areas is called glabrous skin.) All such excision studies agreed in showing no obvious differences among nerve endings taken from regions which responded to different kinds of cutaneous stimulation. In fact, no distinctive or characteristic receptor structures of any type could be seen, and the nerve terminals in the excised regions appeared to be more or less freely ramifying through the skin. These results led investigators to propose that both warm and cold sensations are mediated by free nerve endings, which are of two types, one type responding to cold, and the other to warmth (Dallenbach 1927, Jenkins 1951). In 1928 Pendleton initiated a general study of the neurohistology of human hairy skin as a result of his own failure to locate distinctive receptors in excised skin that displayed a low threshold to cold stimuli. He was unable to find any morphologically complex receptors in hairy regions other than those associated with hair follicles. These findings in their essential features have been confirmed by a number of investigators (Gilbert 1929, Hagen et. al. 1953, Cauna 1959, Winkelmann 1960, Miller et. al. 1960). Thus it is not surprising that no distinctive endings were found beneath low threshold points in human hairy skin, because none are present in hairy regions of the body.

In summary, it can be said that within the limitations imposed by light microscopy there are no strikingly distinctive receptors in human hairy skin other than those associated with the hair follicles. Afferent fibers not innervat-

ing hair follicles ramify freely through the skin. Therefore, whatever specificity of response receptors in such areas may show will not be associated with marked anatomical differences between these receptors. Whether future study with improved methods will reveal anatomical differences is not known. In contrast, well localized and distinctive encapsulated endings are present in glabrous regions. Such ending are found in the skin of the palms of the hands and soles of the feet, at mucocutaneous junctions, and in the mucous membranes of the oral cavity. It is not known whether receptor specificity exists in these regions; and if it does, whether it is correlated with particular anatomical differences in the receptors.

The above discussion has dealt exclusively with experiments on man. The nature of the sensations perceived by animals other than man can only be inferred from non-verbal behavior, but it seems reasonable to assume that an animal such as the cat receives information about tissue damage (pain), about mechanical deformation and movement of the skin, and about the position of its limbs (position sense). Though it is highly probable that the cat can discriminate small changes in skin temperature, this question has not been investigated. The neurohistology of the cat's skin has been studied (Winkelmann 1958), and the findings are in agreement with those on man regarding the distribution of encapsulated endings. The greater density of hair in the cat is associated with an increased hair follicle innervation. In addition, there appear to be differences between man and cat in the structure of encapsulated endings in the glabrous pad skin of the extremities and at mucocutaneous junctions. The functional significance of such differences, if any, is unknown, but their existence suggests caution in generalizing from man to cat.

#### B. Primary afferent fibers and their central connections

The early work of Cajal (1909) demonstrated that cells of the dorsal root ganglia, which are the cells giving rise to primary afferent fibers, vary considerably in size, and that there is a similar variation in the size of their associated fibers. Some of the smallest cells give rise to fibers that have no discernable myelin sheath. Ranson (1911) extended this work by examining peripheral nerves in the cat and other mammals and showed that in cutaneous nerves the myelinated fibers are of many sizes, and that unmyelinated fibers constitute a considerable majority of all the fibers present. Findings such as these raise questions related to the discrimination of modalities of cutaneous



sensation (see Bishop 1959). It may be, for example, that sensations of a particular modality are associated exclusively with activity in fibers of a particular size, or a small range of sizes, and that sensations of other modalities are associated with fibers which are of a different size. On the other hand, it may be that a given modality is associated with activity in fibers that extend throughout the whole range of fiber sizes. It is even possible to imagine that all fibers from a stimulated skin area might be activated if the stimulus were suitably strong. In any case, it would seem likely that the wide range of afferent fiber sizes has some functional significance, and it would be of interest, therefore, to compare the responses of fibers which differ in size.

Another question of interest in connection with the function of cutaneous afferent fibers is the site of their termination in the spinal cord. Cajal (1909), Ranson (1913, 1914, 1915), and Szentagothai (1964) have shown that there is a difference between the organization of small and large afferent fibers after they enter the spinal cord. The large and medium sized myelinated fibers pass into the dorsal columns, whereas the small myelinated and unmyelinated fibers enter Lissauer's tract, or collect just medial to the dorsal root entry zone (see Fig. 2). In all cases the afferent fibers ramify locally in the gray matter of the cord. It is thought that most of the collaterals of the small myelinated and unmyelinated fibers end in the substantia gelatinosa, or around the marginal cells that cap the gelatinosa, the fibers terminating within one or two segments of their point of entry. Collaterals from the larger fibers which enter the dorsal columns appear to terminate locally throughout much of the spinal gray matter, including the gelatinosa. In addition, an ascending division of some and perhaps all of those cutaneous afferent fibers which enter the dorsal columns extends rostrally to the cervical region and terminates in the dorsal column nuclei. From the work of Cajal, Ranson, and Szentagothai, the overall anatomical arrangement can be summarized as follows: 1. There is a separation of large and small fibers as they enter the spinal cord, such that they come to lie in different regions. 2. The dorsal column nuclei appear to receive a projection only from the larger fibers. 3. Unmyelinated fibers end only in the substantia gelatinosa at or near their point of entry into the spinal cord. 4. Considerable overlap may exist in the projection of large and small fibers onto the substantia gelatinosa, the exact nature and extent of this possible overlap being unknown. It would appear that the central

connections of large and small skin afferents are not identical, and it would not be surprising if such anatomical differences were associated with differences in function.

A test for such functional differences might be made if it were possible to sever selectively either the large or the small afferent fibers and then test various skin sensations to determine whether any impairment resulted. It is not possible to make such a section either in the peripheral nerves or at the dorsal root entry zone (Wall 1962, Szentagothai 1964) though the latter procedure was attempted by Ranson and Billingsley (1916a). However, if the dorsal columns are severed, according to present knowledge only large or intermediate sized myelinated primary afferents from levels below the lesion will be interrupted. There may be other ascending fibers in the dorsal columns, since Cajal (1909) has found axons entering this region from cells in the internal basilar nucleus, which is situated on the medial side of the base of the dorsal horn. The destination of these fibers is apparently unknown, but they should not be neglected in evaluating the results of dorsal column transection. The best information regarding sensory loss after such lesions can be obtained from man. Inadvertent interruption of the dorsal columns in man leads to a loss of position sense and the finer aspects of touch (Head and Thompson 1920), including such phenomena as texture and two point discrimination. Perception of thermal sensations and pain is not significantly impaired. When the dorsal columns are transected in the cat, there also appears to be a loss of position sense (Kennard 1954). Whether fine touch or thermal sensations are affected in the cat is unknown, though pain sensations are reportedly not affected by such lesions (Woodward and Sherrington 1904, Ranson and von Hell 1915, Kennard 1954).

If lesions can be made which will abolish position sense and impair touch without any apparent influence on pain or thermal sensations, it is reasonable to ask whether there are lesions which will have the converse effect. In man, after certain unilateral spinal lesions, it has been possible to demonstrate impairment of warmth, cold, or pain sensations without appreciable involvement of touch or position sense (Head and Thompson 1920, White and Sweet 1955). Lesions which are effective in producing this kind of sensory loss are situated in the ventral and lateral white matter of the spinal cord. Each of these sensations (warmth, cold or pain) can be lost independently of the others, though there is often simultaneous impairment of all three. The sensory loss in these

human cases is contralateral to the damaged region of the spinal cord, except at the level of the lesion, where there may be some ipsilateral impairment. The elimination of pain is consistent enough that it is common surgical practice to interrupt fibers in the lateral and ventral white matter of the spinal cord for relief of intractable pain.

The location of lesions which interfere with pain perception in the cat has been subject to controversy. The influence of various lesions on pain sensibility has been examined in this animal by determining the presence or absence of the usual behavioral accompaniments of a painful stimulus, such as struggling and vocalization. It is agreed (Woodward and Sherrington 1904, Ranson and von Hess 1915, Kennard 1954) that dorsal column lesions do not abolish pain. There is also agreement that lateral hemisection of the cord does not abolish pain from either side, indicating that the pathway must be both crossed and uncrossed, in contrast to the situation in humans. Studies in which two lateral hemisections were performed on opposite sides of the cord have uniformly failed to abolish pain in the cat if the hemisections were far enough apart (one at lower thoracic and one at upper cervical) (Ranson and Billingsley 1916a). This last result indicates that pain is conducted at least in part by ascending systems that cross the spinal cord more than once. A final point on which there is good agreement is that complete transection of the spinal cord abolishes pain caudal to the level of transection. However, there is little agreement regarding the position of the pain pathway within the lateral and ventral white matter of the cord. Each of several published studies (Woodward and Sherrington 1904, Ranson and von Hess 1915, Ranson and Billingsley 1916b, 1916c, Kennard 1954) has implicated a different region. The effect of spinal lesions on thermal sensations has not yet been investigated in the cat.

To summarize, evidence exists for a separation of sensory function between the dorsal columns and the lateral and ventral white matter of the spinal cord. Large and intermediate sized myelinated skin afferents are known to enter the dorsal columns and would therefore be implicated in signaling fine touch in man, and perhaps in the cat also. These fibers do not seem to be essential for pain or thermal sensations in man, or for pain in the cat. The small myelinated and unmyelinated fibers which enter the spinal cord and synapse in the substantia gelatinosa can be considered to represent at least a portion of the segmental input to those cells which send their axons

into the ventral and lateral white matter, the interruption of which causes a loss of thermal and pain sensations in man, and a loss of pain in the cat. Therefore, these small fibers are implicated in the transmission of activity giving rise to pain and temperature sensations. It should be noted however, that this evidence is indirect, and that there are difficulties in interpreting the results of lesion experiments. For example, there may be several pathways necessary for the performance of a certain sensory function, some having a much more specific relationship to that function than others, but interruption of any of the pathways might result in a loss of the sensory capacity. In any case, lesion experiments do not indicate whether thermal sensations and pain are mediated over the same or different fibers either in peripheral nerves or in the spinal cord.

## II. Electrophysiological Studies

For some time techniques permitting the study of single primary afferent fibers have been available, and in recent years microelectrode methods have been developed for the study of single units in the central nervous system. These techniques are potentially powerful tools for analyzing mechanisms of cutaneous sensations. By recording from single cutaneous primary afferent fibers and subjecting the skin to a variety of stimuli, it should be possible to determine the range of response of a particular receptor. By recording from single postsynaptic elements in the spinal cord and brain it should be possible to determine whether there has been any loss or gain in the specificity of primary afferent activity as it is relayed to higher centers. Information about the temporal pattern of activity in single sensory units can also be obtained with these methods. Various aspects of temporal patterning can be considered. One concerns the degree to which discharge is regular or irregular. When a discharge is very regular successive interspike intervals differ little; when the discharge is very irregular then they differ greatly; and all intermediate states between very regular and very irregular might be seen. Variability of discharge frequency with time is most often employed to describe degree of regularity or irregularity, but the interval over which the frequency is calculated must be carefully specified in such cases. For example, if all impulses in successive seconds of time are counted for many seconds, all the values may be much the same, but it will not be known whether the impulses occur in a regular sequence, or whether short bursts of impulses lasting perhaps a few tenths of a second occur separated by periods of no activity. If the

counting had been done over a period of 50 msec., then the values for consecutive 50 msec. periods could differ greatly. Thus, in determining whether a discharge is regular it is necessary to count the number of spikes occurring in a short interval. It is still better to take each successive interval and compare it quantitatively with that just preceeding.

Another aspect of the temporal pattern of sensory activity is related to whether frequency of discharge changes with time following application of a stimulator. Some receptors continue to discharge for as long as the stimulator is in contact with the skin, whereas others cease discharging even though the position and temperature of the stimulator do not change. A sensory response which shows no decline while the stimulator is unvarying is said to be nonadapting, a sensory discharge which occurs only during changes in the position or temperature of the skin is said to be very rapidly adapting: various intermediate types exist.

Many sensory responses are influenced by the rate of application of the stimulator (mechanical or thermal). Generally, the frequency is higher the more rapidly the stimulator is applied, and such a response is said to show "velocity sensitivity". This phenomenon can be so conspicuous that gradual application of a mechanical stimulator to mechano-sensitive receptors elicits no activity at all, whereas rapid application of the same stimulator causes a high frequency burst of impulses, the final position of the stimulator being the same in both cases. Velocity sensitivity is a mechanism for signaling transients, there being a partial or complete filtering of non-transients depending on the degree of adaptation of the response.

Other aspects of temporal patterning might be discussed, but in the present experiments only those outlined above will be considered. In the review of the electrophysiology of somatic sensation which follows, attention will first be given to studies of primary afferent fibers, and then to studies of activity recorded post-synaptically in the spinal cord and brain stem. The experiments of primary afferent fibers can be divided roughly into two periods: work done prior to 1940, and work done after 1950. Experiments prior to 1940 were carried on by two laboratories, those of Adrian and Zotterman. In most of these early experiments recordings were made from multifiber preparations, and while they served to establish some of the basic principles of sensory physiology, it was not possible to make unequivocal tests of the specificity of individual receptors. In more recent studies, which have been conducted

by a number of different investigators, recording from single units has been emphasized, and as a result more information has been obtained concerning the range of stimuli to which a particular receptor is responsive. In virtually all this work the cat has served as the experimental animal, and unless otherwise stated the data presented will apply to this animal. As will be evident from the ensuing discussion, certain receptors have been found to respond to stimuli associated with more than one sensory modality. Receptors of this type have nevertheless been arbitrarily referred to as "specific" if they respond to stimuli of one modality with a discharge the maximum frequency of which is 10 times greater than the maximum frequency which occurs in response to any other stimulus.

### Electrophysiology of primary afferent fibers

#### I. Early work of Adrian and collaborators

##### A. Mechano-sensitive receptors

Studies of the responses of single primary afferent fibers and small multifiber strands were not possible before the development of vacuum tube amplifiers and low inertia display systems (Adrian 1926, Matthews 1928). By the mid nineteen twenties suitable instruments had become available and the first investigations were undertaken. It was soon discovered that mechano-sensitive receptors in both skin and muscle fired at higher frequencies when they were stimulated with greater force (Adrian and Zotterman 1926a, 1926b). Since it could be seen that not all receptors supplying a given region had the same threshold, increasing the strength of the stimulus also resulted in activation of a larger number of receptors. The spike size in any give afferent fiber appeared to have an all or nothing relationship to the stimulus, which meant that differences in nature or strength of stimulus could not be signaled by differences in sizes of individual spikes. The first clear demonstration of the above principles came from the work of Adrian and Zotterman (1926a) on the muscle spindle of the frog. They activated the receptor by stretching the muscle in which the receptor lay, and succeeded in obtaining preparations in which only one fiber was active. It is only when recording from single units that one can clearly see the way in which the sensory response varies with the type and extent of the stimulus. The implications of these findings for cutaneous sensory physiology have been lucidly discussed by Adrian (1931) who pointed out that the only way in which information can be transmitted in the somatosensory system is by varying the temporal sequences of impulses in active fibers and

by varying the total number of fibers responding.

Adrian and his collaborators also demonstrated that mechano-sensitive receptors in the skin vary in their rate of adaptation. Recording from small multifiber strands, they found that some receptors when stimulated mechanically ceased to discharge as soon as movement of the stimulator ceased. There were units of this type in the cat which were well activated by hair movement. Other cutaneous receptors gave a persistent discharge to steady pressure, although the frequency of this discharge declined gradually while the position of the stimulator was maintained. A similar slowly adapting type of activity had been seen in afferent fibers from muscle spindles. In addition, velocity sensitivity in response to mechanical stimulation was observed. This was most striking in the case of rapidly adapting cutaneous receptors, where no discharge whatever occurred if the stimulator was applied sufficiently slowly. In the case of slowly adapting cutaneous and muscle spindle receptors, the maximum frequency of discharge was much reduced by applying the stimulator gradually. A final observation was that the muscle spindle discharged in a regular fashion when subjected to steady pull, whereas the discharge of slowly adapting mechano-sensitive skin receptors was rather irregular in response to steady mechanical displacement.

These early observations established some of the fundamental properties of mechano-sensitive receptors which can be summarized as follows: frequency of discharge is proportional to the velocity and force with which the stimulator is applied; certain receptors adapt slowly, others adapt rapidly; and some receptors discharge in a regular fashion, while others discharge in a much less regular way at comparable frequencies. The functional significance of these properties for the transfer of information from the environment has yet to be clarified, and insight into their functional role is not likely to be obtained until more is known about the way in which the central nervous system is processing the information it receives.

#### B. Receptors responding to noxious stimuli

In addition to studying afferent activity elicited by gentle and moderate mechanical stimulation, Adrian also attempted to record responses to various noxious stimuli. In man, when the skin is damaged by burning or crushing, there is a marked sensation of pain which occurs while the skin is being injured, and following the injury there is a persistence of the sensation for some time, while the damaged region becomes hyperalgesic. The term hyperalgesia denotes a con-



dition in which cutaneous stimuli which do not normally cause pain are able to do so. When acid is put on the skin of a human subject there is a gradual development of the sensation of pain and this increments until the stimulus is removed. Adrian (1931) applied these types of stimuli to the skin of the cat while recording from small filaments of cutaneous nerves. He did not record from filaments small enough to contain only a single active fiber and so was unable to test the responses of single receptors to noxious stimuli. Nevertheless, it was clear that the afferent response to noxious stimulation of the skin was neither particularly large nor well maintained. For example, when a crushing stimulus was applied to the skin the initial discharge ceased rapidly, even though the pressure was maintained; and when acid was applied to the skin, virtually no discharge whatever was recorded. In attempting to account for these puzzling findings, Adrian noted that Erlanger and Gasser (1930) had shown that unmyelinated (C) fiber action potentials were small when recorded extracellularly. In fact, the smaller a fiber, whether myelinated or not, the more slowly it conducts, and the smaller its extracellularly recorded action potential. Adrian could see no evidence in any of his recordings for action potentials conducted at velocities as low as those characteristic of C fibers; and though action potentials occurred to varying extents in both small and large myelinated fibers when noxious stimuli were applied, in no case did their discharge correlate with the time course and intensity of the pain sensations which the stimuli would have evoked in man. In interpreting these negative results, Adrian assumed it was likely that "pain" fibers were activated similarly in both cat and man, and that these fibers in the cat were too small to record from with the techniques employed.

Results obtained on the frog (Adrian 1931) supported this interpretation. In this animal it was possible to record, in multifiber preparations, the activity of small fibers whose response to damaging stimuli correlated quite well in intensity and time course with similarly elicited pain in man. These fibers were probably small myelinated afferents, though perhaps some of the larger unmyelinated fibers were also included. The recorded activity was characterized by a slow rate of adaptation to maintained crushing stimuli, to heating, and to acid. After the removal of these stimuli, the discharge persisted for some time. Scraping the skin with a scalpel also led to a persistent discharge in these fibers, which thus seemed better candidates than any previously studied for participation in a primary afferent system eliciting the sensation of pain.



This slowly conducting system of sensory fibers in the frog has been the subject of a number of papers from the physiological laboratory at Cambridge (Feng 1933, Hogg 1934, Echlin and Propper 1937, Hahgood 1950). Feng showed in both cat and frog that cutaneous receptors which have low thresholds to mechanical stimulation and large myelinated afferent fibers are inactivated by stimuli which damage the skin. The slowly conducting afferent fibers in the frog, on the other hand, are not inactivated by such damage unless it is severe. In fact, as Echlin and Propper showed, appropriate damage to the skin tends to increase the responsiveness of the slowly conducting afferents to a standard mechanical stimulus. This lends further support to the notion that slowly conducting fibers are concerned with pain, since some such sensitization of pain afferents would be expected in hyperalgesic skin. Furthermore, it is difficult to imagine the large fibers participating in the pain response since they are unable to respond after the skin is damaged.

It should be noted that in none of these studies of small afferent fibers were single unit preparations obtained. Hogg (1934) did succeed in recording the activity of single slowly conducting fibers responding to noxious mechanical and thermal stimulation by using the technique of recording in a multifiber strand, but restricting the stimulus to a small spot. Unfortunately, such methods do not permit the testing of the responses of single receptors to a number of different stimuli, and Hogg was not able to determine whether the same fiber was able to respond to both damaging mechanical and damaging thermal stimuli. Still, in spite of this limitation, the experiments by Adrian and his students on the frog represent a prototype for any experiments done on pain afferents.

## II. Early work of Zotterman

### A. Mechano-sensitive receptors

Zotterman (1939), extending the work of Adrian, studied for the first time the responses of small cutaneous afferent fibers in the cat, and although no single unit recordings were made, it was clearly demonstrated that even gentle mechanical stimuli delivered to hairs resulted in the activation of afferent fibers of many sizes. Large myelinated fibers responded, as well as small myelinated and unmyelinated ones. In fact, the small myelinated and unmyelinated fibers responded to weaker mechanical stimuli than the large myelinated fibers. This result is important because it indicated that it is not possible to associate mechanical stimulation with activity in afferent fibers of any particular size. It should

be understood, however, that the sensations elicited by mechanically evoked activity in large and small fibers need not be identical. In man, gentle mechanical stimuli cause sensations of itch and tickle as well as touch. Zotterman noted that the stimuli which exclusively activated the small myelinated and unmyelinated fibers were similar to those that cause itching and tickling sensations in man, and considered it likely that small myelinated and unmyelinated fiber discharge was associated with such sensations. This suggestion was further supported by the fact that after-discharge occurred in the small fibers following mechanical stimulation, and by the fact that activity in some of these fibers was depressed by non-injurious rubbing of the skin.

#### B. Receptors responding to noxious stimuli

Zotterman (1939) found that small myelinated and unmyelinated cutaneous afferent fibers in the cat were activated by a variety of damaging stimuli applied to the skin (crushing, heating, acid), whereas the larger myelinated fibers were not. Similarly, activity occurred in small myelinated fibers of the cat lingual nerve during noxious stimulation of the tongue (Zotterman, 1936), and in this instance also the larger myelinated fibers were not stimulated. The small fiber discharge was maintained throughout the period of damaging stimulation and persisted following the removal of the stimulator, thus displaying a time course similar to the pain which would be experienced by human subjects following such stimuli. These results, obtained by Zotterman using the cat, correlate well with those of Adrian and his collaborators on the frog, and suggest that noxious stimuli activate exclusively small myelinated and non-myelinated fibers. Whether individual small fibers responding to gentle mechanical stimuli in the cat also respond to noxious stimuli could not be determined because no single unit recordings were obtained.

### III. Summary of early work

Although the experiments discussed thus far have been done almost exclusively on multifiber preparations, the following points have emerged: 1. In the frog the receptors with the lowest threshold to mechanical stimulation appear to be rapidly adapting and associated with large fibers. 2. In the cat there are low threshold mechano-sensitive receptors associated with both large and small myelinated fibers and with non-myelinated fibers. 3. In both the cat and the frog damaging stimuli tend to inactivate the large fiber, low-threshold mechano-sensitive elements, and at the same time provoke a discharge in small myelinated and unmyelinated fibers. In addition, a damaging stimulus

to the skin of the frog lowers the threshold of the small fibers to mechanical stimulation, a point which does not seem to have been investigated in the cat.

#### IV. Single Unit Studies

##### A. "Specific" Thermo-sensitive Receptors

##### 1. Thermo-sensitive receptors associated with myelinated fibers

Zotterman and his collaborators have shown in a number of investigations (Hensel and Zotterman 1951a, 1951b, 1951c, 1951d, 1951e, Dodt and Zotterman 1952a, 1952b, Dodt 1953, Hensel 1953a, 1953b, Hensel and Witt 1959) that small myelinated fibers in the lingual nerve of the cat change their frequency of discharge when the temperature of the tongue is altered. The discharge which occurred in these fibers in response to a change in temperature had a transient initial component which was determined by the direction of the temperature change (whether the skin was warmed or cooled), by the magnitude of the temperature change, and by the rate at which the temperature change occurred; and a later steady state component which was determined only by the final temperature reached. Some fibers, called "cold" fibers, showed a transient increase in frequency when the temperature was lowered and were transiently inhibited by an elevation in temperature. Other fibers, called "warm" fibers, which seemed to be present in smaller numbers, showed just the opposite behavior, there being a transient increase in frequency when the temperature was raised and a transient decline in frequency or cessation of discharge when the temperature was lowered. If the temperature of the tongue surface changed rapidly, or through a wide range, the initial discharge was of a considerably higher frequency (or the initial inhibition was more profound) than when the temperature was changed slowly, or through a narrow range. The sensitivity of the receptors was great, a  $0.1^{\circ}\text{C}$  change in the temperature of the tongue surface being sufficient to evoke a response. The steady state component of the response was characterized by a frequency of discharge considerably lower than that which could occur during the initial phase. The temperature dependence of this steady state component differed somewhat in cold and warm fibers. In cold fibers the highest frequencies occurred when the temperature of the skin surface was maintained between  $20^{\circ}\text{C}$  and  $35^{\circ}\text{C}$ . For each individual cold fiber there was a particular temperature between  $20^{\circ}\text{C}$  and  $35^{\circ}\text{C}$  at which the frequency of discharge was highest, the steady state frequency declining when the temperature was either raised or lowered from this optimal value, until a temperature was reached at which no steady state response whatever occurred. The total temperature range over which particular cold fibers

responded with a non-adapting discharge was twenty to thirty degrees. The steady state component of the warm fiber response behaved similarly except that optimal temperatures were higher ( $38^{\circ}\text{C}$ - $43^{\circ}\text{C}$ ) and the total range over which the response occurred in a particular fiber was smaller, being ten to twenty degrees.

Receptors activated by cooling also responded with a non-adapting discharge when the temperature of the tongue surface was raised to  $45^{\circ}\text{C}$ - $50^{\circ}\text{C}$ . This was thought to correspond to the "paradoxical" cold sensation that results in man when points on the skin particularly sensitive to cold are heated. Psychophysical studies had also led to the characterization of a "paradoxical" warmth, which occurred when regions of the skin especially sensitive to warmth were cooled. In this case, too, a parallel was found in for it was noted that strong, sudden cooling could cause a transient discharge in warm fibers.

Another point of importance with regard to these thermally sensitive receptors was that they did not respond readily to mechanical stimuli. At best, strong mechanical stimulation evoked only a weak discharge. Also, these receptors did not respond to either strong heating or extreme cooling. Temperatures above  $50^{\circ}\text{C}$  or below  $10^{\circ}\text{C}$  did not activate them. In fact, both warm and cold fibers were inactivated by strong heating. Zotterman and collaborators considered it likely that these receptors were concerned with transmitting information about small non-noxious temperature changes, and that they were specific for that function. The rather striking parallel between the behavior of these afferents and the thermal sensations experienced by man was considered to support this view, and the data were interpreted as supporting the concept that there are specific receptors for cold and warmth.

## 2. Thermo-sensitive receptors associated with unmyelinated fibers

The thermally sensitive receptors in the cat's tongue described by Zotterman and collaborators were associated with small myelinated fibers. Similar fibers have been described by Hensel (1952) innervating the skin of the face, but no myelinated fibers with such properties could be found supplying the general body skin of the cat (see Witt and Hensel 1959). It is known that unmyelinated fibers are much more numerous in spinal nerves than in cranial nerves (Ranson et. al. 1935), and the possibility existed that in spinal nerves "specific" thermo-receptors might be associated with unmyelinated fibers. That such is the case has been shown by Hensel, Iggo and Witt (1960). These investigators described receptors associated with unmyelinated fibers which responded to

very slight changes in skin surface temperature ( $0.1^{\circ}\text{C}$ ) and which fell into two groups: those responding to cooling and inhibited by warming, and those responding to warming but inhibited by cooling. In almost all respects these afferent fibers behaved in response to thermal stimuli like the small myelinated "warm" and "cold" fibers studied earlier by Zotterman and his co-workers. The C fibers also resembled the "specific" cold and warm lingual fibers in showing almost no response to mechanical stimulation. Iggo (1963b, 1964) has made similar observations while recording from afferent fibers innervating the general body skin of the monkey, but in this species cutaneous "cold" and "warm" receptors were found to be associated with small myelinated fibers.

### 3. Summary of "specific" Thermo-sensitive Receptors

Receptors exist in the cat, associated with small myelinated fibers in regions innervated by cranial nerves, and associated with C fibers in regions innervated by spinal nerves, which can respond either to small increases or small decreases in skin temperature, and which do not respond readily to mechanical stimulation. These receptors are inactivated by strong heating. They have the properties one might expect of specific "warm" and "cold" afferent fibers.

#### B. "Specific" Mechano-sensitive Receptors

##### 1. Mechano-sensitive receptors associated with myelinated fibers

In discussing mechano-sensitive receptors associated with myelinated fibers it is useful to consider separately the hairy regions of the body and glabrous pad skin. This is because the hairs themselves are tactile organs. It will be seen that rapidly and slowly adapting mechano-sensitive receptors are present in both hairy and glabrous regions. Slowly adapting mechano-sensitive receptors are associated with small "spot-like" receptive fields in all cases, and respond not only to mechanical stimulation but also to thermal stimuli. Rapidly adapting receptors are associated with hairs where these are present, but are also found in glabrous pad skin. The vibrissae are an exception since they have been found to be associated with slowly adapting receptors (Fitzgerald 1940), and they will not be considered further. Irrespective of location, rapidly adapting receptors have been found to be unresponsive to thermal stimuli.

"Specific" Mechano-sensitive Receptors associated with  
myelinated fibers in hairy skin

a. Rapidly adapting receptors in hairy skin

The only rapidly adapting myelinated fiber receptor which has been reported in significant numbers in cat hairy skin is termed the "hair" receptor. The behavior of these receptors is quite simple (Witt and Hensel 1959, Hunt and McIntyre 1960b). Moving the hairs of the receptive area was found to be the most effective stimulus, and stimulating the skin in addition to hairs did not result in further activation. The receptors responded only to movement of the hairs and were thus of the very rapidly adapting type. There was no response to thermal stimuli. As would have been anticipated from the earlier work of Zotterman (1939), "hair" receptors were associated with myelinated fibers of many sizes, individual conduction velocities ranging from 90 m/sec to 10 m/sec (Hunt and McIntyre 1960b). The receptive fields of dorsal column "hair" units innervating the hindlimb have been found to vary in size according to their position on the limb (Yamamoto, Sugihara and Kuru 1956), the smallest receptive fields being located on the toes, the largest on the thigh. The smallest digital receptive fields are sufficiently small to be referred to as "spot-like" while the areas of the largest fields on the thigh were about 100 times greater. Further information concerning "hair" unit receptive field sizes, and the general significance of the concept of receptive fields will be considered when the results of the present experiments are discussed.

b. Slowly adapting receptors in hairy skin

Slowly adapting mechano-sensitive receptors in cat hairy skin, associated with myelinated fibers, have invariably been found to possess small, spot-like receptive fields. The earliest description of receptors of this type appears to be that of Frankenheuser (1949). More recently studies have been made by Witt and Hensel (1959), Hunt and McIntyre (1960a), Iggo (1963) and Tapper (1964). These receptors were found to have no resting discharge at neutral skin temperatures (30° approximately), but showed an increased excitability at elevated temperatures which sometimes led to the appearance of a resting discharge at skin temperatures of 40°C or above (up to 43°C - 44°C) (Hunt and McIntyre 1960a). Receptors of this type were transiently activated by a rapid fall in temperature and transiently inhibited by a rapid increase in temperature, though they were much less sensitive to such stimuli than the "specific" cold receptors described above. The receptors discharged in an irregular fashion.

The experiments of Witt and Hensel (1959) have shown that there are at least two types of slowly adapting receptors in hairy skin. One type, by far the most common, is that described above. The second type could be distinguished from the first because it possessed a low frequency resting discharge at neutral skin temperatures, and because the receptor discharged in a comparatively regular fashion. The resting discharge could be modified by altering the temperature of the skin, and the receptors behaved like the "specific" thermal fibers described earlier in showing a maximum resting discharge at a particular temperature, the discharge declining as the temperature was either elevated or lowered from this value, until all resting activity ceased when the temperature moved beyond the effective range. Units of this type were transiently activated by cooling and transiently inhibited by warming, but the change in temperature had to be of some magnitude before any response occurred. Although these receptors behaved in a general way like specific "cold" receptors in response to thermal stimuli, they differed from cold receptors by being considerably less sensitive to thermal stimuli and far more sensitive to mechanical stimulation.

Quantitative comparisons of the maximum frequencies of discharge that can be obtained in slowly adapting units with thermal and mechanical stimuli have shown (Iggo 1963) that frequencies of discharge between 600/sec and 1000/sec could occur in response to moderate pressure applied rapidly to the receptive spot, whereas the maximal discharge that could be obtained with rapid cooling was less than 10% of this value (50/sec., see also Hensel and Zotterman 1951f). On this basis these receptors have been provisionally classified as mechanoreceptors. If it could be shown that mechanical stimulation produces a different pattern of activity than that resulting from thermal stimuli, then classification of the receptors would be more difficult. This question will be considered further when the results of the present experiments are discussed.

Iggo had noted that the slowly adapting receptors in hairy skin were velocity sensitive, and this aspect of their response has been systematically studied by Tapper (1964). Tapper used defined mechanical stimuli, independently varying both the rate of application of the stimulator and its final position. It was found that the units were driven to highest frequencies (up to 1000/sec for a short time) by a rapidly moving stimulator, and that over a considerable range of velocities the more rapidly the stimulator displaced the skin the higher the frequency of the response.

A final question of interest concerns the structure of the slowly adapting receptors in hairy skin. Hunt and McIntyre (1960b) found units of this kind to be associated only with the larger myelinated fibers (conduction velocities ranged from 50 m/sec to 90 m/sec). Often more than one spot-like receptive field



was innervated by a single fiber. Iggo (1963) has shown that these sensitive spots are associated with small elevations on the skin, and that these elevations have a characteristic structure. They are more highly vascular than surrounding skin areas, and the myelinated fiber (only one is seen) which enters the elevation is associated with "receptor" cells typical of a Merkel's disc. In Merkel's discs the myelinated stem fiber breaks up into non-myelinated terminals which end in close contact with specialized epithelial cells in the basal layer of the epidermis. Cauna (1959, 1961) has illustrated this type of receptor particularly clearly using both silver methods and electron microscopy. It would not be correct to call this an encapsulated ending of the sort seen in glabrous skin, but nevertheless it is a type which can be distinguished morphologically from other receptors. Thus it would appear that in the case of these receptors, a characteristic response can be associated with a characteristic receptor type, though paradoxically the behavior of this receptor is not entirely specific.

**"Specific" mechano-sensitive receptors in glabrous foot pad skin  
associated with myelinated fibers**

Receptors in glabrous pad skin, have been less thoroughly studied than those in hairy skin. Slowly adapting myelinated fiber receptors apparently have not been investigated since the work of Adrian and Zotterman (1926b) on pressure receptors in the foot pad. In the present experiments the properties of these slowly adapting receptors have been further studied and will be described in detail later. Briefly, it may be said that the receptors from which recordings have been obtained resemble in their responses to mechanical stimuli, thermal stimuli, and receptive field deminsions, the most common slowly adapting units in hairy skin.

Rapidly adapting cutaneous receptors in the foot pads have been investigated by Armett and Hunsperger (1961), as well as in the present experiments. Armett and Hunsperger activated these receptors in a rather restricted fashion, using single, very brief mechanical pulses. In the present experiments somewhat cruder, but more physiological, mechanical stimuli have been used, as well as thermal stimuli. Anticipating somewhat, it may be said that the receptors respond only to movement of the pad skin, that they respond at highest frequencies to high velocity mechanical stimulation, and that they are unresponsive to thermal stimuli. Receptive fields were found to be considerably larger than those associated with slowly adapting receptors in pad skin.



## 2. "Specific" mechano-sensitive receptors associated with unmyelinated fibers

C fiber mechano-sensitive receptors in glabrous skin have not been studied, and the present discussion will therefore be limited to receptors in hairy skin. Confirming earlier work by Zotterman (1939), it has been found (Iggo 1959, 1960) that a range of mechanical stimuli is effective in exciting unmyelinated afferent fibers, and on the basis of threshold to mechanical stimulation Iggo has divided mechano-sensitive C fiber receptors into the following 3 categories: 1. A group of receptors having very low thresholds to mechanical stimulation; 2. receptors responding when pressure on the receptive area became moderately strong, though not strong enough to have been noxious; 3. receptors requiring strong, probably noxious pressure before any discharge occurred. Some of the receptors in the first category responded to hair movement, others responded only to direct stimulation of the skin. Receptors of the third type might be considered nociceptors were it not for the observation that they, like receptors in the first and second categories, were temporarily inactivated by brisk rubbing of the skin. All the receptors adapted rather rapidly, the response to maintained deformation of the skin lasting at most about 30 seconds; and all showed an after-discharge. Iggo found that C fiber mechano-sensitive receptors responded to rapid cooling with a weak transient discharge. Some receptors also responded to heating, rather high and probably noxious temperatures being required before any discharge occurred. The response to high temperatures consisted of a brief high frequency burst of impulses, after which the receptor was inexcitable. Because the maximal discharge which occurred in response to cooling was much less than the maximal mechanically evoked discharge, and because the response to heating appeared to be associated with damage, all these receptors were classified as mechanoreceptors.

## 3. Summary of "specific" mechano-sensitive responses

1. There are myelinated fiber receptors in both the hairy and glabrous pad skin of the cat which respond to movement but not to maintained displacement of the skin (very rapidly adapting), and which do not respond to temperature changes. In hairy regions such receptors are as effectively activated by hair movement as by direct mechanical stimulation of the skin.
2. There are myelinated fiber receptors in both hairy and glabrous skin which display velocity sensitivity in response to a moving stimulator, and which res-

spond in a maintained fashion to maintained displacement of the skin. Receptors of this type exhibit a transient low frequency discharge in response to rapid cooling and are transiently inhibited by an increase in temperature. They are associated with small spot-like receptive fields. Two types of receptors with the above properties seem to exist. One type is numerous, shows no resting discharge at neutral skin temperatures, but displays an increase in excitability at steady elevated temperatures. The second type is scarce, and displays a low frequency resting discharge at neutral skin temperatures, a discharge which is temperature dependent. 3. There are receptors associated with unmyelinated fibers which are highly sensitive to mechanical stimulation, others which are only moderately sensitive, and some of which are quite insensitive. These receptors respond to maintained displacement of the skin with a discharge which ceases after a few seconds. They are rendered temporarily inexcitable by brisk rubbing of the receptive area. A weak, transient discharge occurs in response to the rapid cooling, and heating produces a brief discharge prior to inactivation.

#### C. Receptors responding "specifically" to noxious stimuli

##### 1. "Specific" nociceptors associated with myelinated fibers

There are few reports of myelinated fiber activity initiated by damaging stimuli in spinal cutaneous nerves (see Hunt and McIntyre, 1960b). There has been some success, however, in recording activity in response to such stimuli from small myelinated fibers in cranial nerves. Zotterman's (1936) studies of lingual receptors have already been discussed. Pfaffman (1939) found in the cat that a persisting discharge appeared in small myelinated fibers innervating teeth which had been damaged by breaking, and also following application of hot or cold water to the teeth. Bowman (1959) found that small myelinated fibers innervating face skin in the rat were activated by cooling the skin below 25°C. Since clear single unit recordings were not obtained by these investigators, precise determinations of the response properties of the receptors could not be made. Nevertheless, it was thought likely that these receptors conveyed information concerning tissue damage.

##### 2. "Specific" nociceptors associated with unmyelinated fibers

Unmyelinated fibers associated with receptors which respond exclusively to damaging stimuli have been found in both cranial nerves (innervating the tongue) and in the spinal nerves (innervating hairy skin). According to Iggo (1959), two different types of C fiber receptors responsive to noxious stimuli can be seen in regions innervated by the saphenous nerve. One type responded when the

skin was strongly heated (above  $45^{\circ}\text{C}$ ), and the other type responded when the skin was strongly cooled (below  $10^{\circ}\text{C}$ ). Both types discharged in a maintained fashion to their appropriate stimuli. The receptors were rather insensitive to mechanical stimulation, though strong mechanical stimuli could evoke a weak rapidly adapting discharge.

Somewhat less specific high threshold C fiber receptors have been described by Iriuchijima and Zotterman (1960, 1961) in the tongue and hairy skin of the cat. These investigators found that individual receptors responded in a maintained fashion to both strong heating (above  $50^{\circ}$ ) and strong cooling (below  $10^{\circ}$ ), and that they were not readily activated by mechanical stimuli. These observations, coupled with those of Iggo, indicate that C fiber receptors responding to extremes of temperature are heterogenous, though all are characterized by the fact that they are not depressed or inactivated by extreme temperatures. Because they respond only weakly and in a transient fashion to even vigorous mechanical stimuli, these receptors can be provisionally classified as thermal nociceptors.

### 3. Summary of receptors responding "specifically" to noxious stimuli

1. There are C fiber receptors which respond with a steady discharge to either strong heating or strong cooling, but not to both, being activated rather than inactivated by such stimuli. These receptors are not readily driven by mechanical stimulation. 2. There are C fiber receptors which respond in a maintained fashion to both strong heating and strong cooling, and are resistant to inactivation by such stimuli. They also are not readily activated by mechanical stimulation. 3. There are receptors associated with small myelinated fibers in regions innervated by cranial nerves which respond to damaging stimuli of various kinds, the specificity of individual receptors being as yet undefined.

### D. "Non-specific" Receptors

Witt (1962) has described C fiber receptors which are clearly activated in a non-specific fashion. These receptors responded to weak mechanical stimuli, rapid cooling, and strong heating. The frequency of discharge was similar in response to any one of these stimuli, and classification of these afferents in terms of a most effective stimulus would be impossible. No attempt was made to compare quantitatively the patterns of discharge in these fibers to different stimuli, and just what their functional significance might be is at present a

matter for conjecture. Unless it can be shown that distinctive patterns of activity occur in response to different stimuli, it would be difficult to imagine such fibers solely responsible for the signaling of pain because weak mechanical stimuli are as effective in activating them as strong heating.

#### V. General Summary of Primary Afferent Activity

According to present evidence only the larger myelinated cutaneous sensory fibers are, as a group, activated predominantly by one kind of stimulation, in this case mechanical. Small myelinated and unmyelinated fibers can be activated by mechanical, thermal, and damaging stimuli, though individual fibers tend to respond primarily to stimuli of only one kind.

##### A. Mechanoreceptors

1. Hair movement causes activity in myelinated fibers which extend throughout the afferent spectrum, and in unmyelinated fibers. The receptors which are associated with myelinated fibers respond only to hair movement, whereas those associated with unmyelinated fibers adapt somewhat more slowly, and in addition show a low frequency after-discharge. Presumably sensory nerve fibers which terminate around hair follicles constitute the morphological "hair" receptor. Both myelinated and unmyelinated sensory fibers have been seen innervating the same follicle (Winkelmann 1958).

2. Direct mechanical stimulation of the skin causes activity in the larger myelinated fibers and in unmyelinated fibers, in addition to activating receptors sensitive to hair movement. Direct stimulation of glabrous skin activates myelinated fiber receptors which are very rapidly adapting, resembling myelinated fiber "hair" receptors in many respects. In both hairy and glabrous regions direct stimulation of the skin activates slowly adapting myelinated fiber receptors which have many similar properties, one of which is irregular discharge. The receptor structure associated with the slowly adapting type of response in hairy skin has been identified histologically and shown to be a Merkel's disc. Such identifications have not been made for any receptors in glabrous skin. Unmyelinated fibers activated by direct mechanical stimulation of hairy skin vary in threshold, some responding to gentle or moderate stimuli, others only to damaging stimuli. All the C fiber receptors adapt moderately rapidly, are temporarily inactivated by brisk rubbing of the skin (as were C afferent "hair" units), and show a low frequency after discharge. C fibers are considered to form only "free" nerve endings in the skin.

3. Very rapidly adapting mechano-sensitive receptors do not respond to thermal stimuli.

4. Slowly adapting myelinated fiber mechano-sensitive receptors behave like insensitive "cold" fibers in response to temperature changes, but typically do not respond in a tonic fashion to maintained lowered temperatures.

5. Some unmyelinated mechano-sensitive fibers respond to rapid cooling with a weak transient discharge, and some respond to strong heating with a transient high frequency response prior to inactivation.

#### B. Thermoreceptors

1. Receptors sensitive to small changes in temperature have been found associated with small myelinated fibers in the trigeminal nerve (a cranial nerve) and unmyelinated fibers in hindlimb cutaneous nerves. The receptors respond to both temperature changes and to maintained alterations in skin temperature. They are of two types. "Warm" fibers which are excited by an increase in temperature, and "cold" fibers which are excited by a decrease in temperature. Though no definite information is available, presumably the unmyelinated "warm" and "cold" fibers end "freely" in the skin, and this may be true for the cranial fibers as well.

2. Thermoreceptors do not respond readily to mechanical stimuli.

3. There seems little doubt that thermoreceptors are associated exclusively with fibers of a particular size, these being small myelinated fibers in cranial nerves (where unmyelinated fibers are less numerous than in spinal nerves) and unmyelinated fibers in hindlimb cutaneous nerves.

#### C. Nociceptors

1. There are receptors associated with small myelinated and unmyelinated fibers in cranial nerves and unmyelinated fibers in hindlimb cutaneous nerves which respond either to strong heating, strong cooling, or both. They respond in a maintained fashion to the effective stimuli. The unmyelinated fibers presumably form "free" nerve endings, and this may be true of the small myelinated fibers as well.

2. These receptors are not readily activated by mechanical stimulation.

3. Nociceptors appear to be associated exclusively with fibers of a particular size, which are small myelinated or unmyelinated in cranial nerves and unmyelinated in hind limb cutaneous nerves.

#### D. Non-specific receptors

1. Receptors have been described, associated with unmyelinated fibers, which respond vigorously to gentle mechanical stimulation, strong heating, and rapid cooling. The functional significance of these receptors is uncertain.

### Electrophysiology of Post-synaptic Neurons in the Central Nervous System

#### I. Post-synaptic elements in the Trigeminal Nucleus

Although considerable evidence exists for specificity in the responses of primary afferent fibers to different kinds of cutaneous stimuli, there is nevertheless the possibility that, as a result of convergence, post-synaptic units in the central nervous system respond to more than one kind of stimulation. It should be possible to determine whether or not such convergence occurs by recording from single post-synaptic neurons while delivering the appropriate stimuli to the skin. Only a few investigations have been concerned with the question of the extent to which post-synaptic elements are activated in a specific fashion by cutaneous stimuli, and most of these have been conducted on the trigeminal nucleus. This nucleus receives cutaneous afferent fibers from the fifth cranial nerve, fibers which are considered to convey information related to general somatic sensibility from the skin of the face and mucous membranes of the oral cavity. The fibers enter the brain stem and form the trigeminal tract, which projects both rostrally and caudally, before ending in synaptic relation to the cells of the trigeminal nucleus. On the basis of clinical findings it has been proposed that the caudal part of the nucleus is concerned with thermal sensations and pain, and that the more rostral parts of the nucleus are concerned with touch sensations (see Walker 1939). The evidence for this view is derived mainly from observations on patients with transections of the caudal projection of the trigeminal tract. Such transections, even when made quite caudally in the brain stem, abolish sensations of pain and temperature from the face without markedly interfering with the appreciation of touch. Anatomical studies have provided further suggestive evidence that the caudal part of the trigeminal nucleus might be concerned with pain and temperature (Olszewski 1950). It was observed that the lateral portion of the caudal part of the trigeminal nucleus was very similar in structure to the substantia gelatinosa of the spinal cord, whereas more rostral parts of the trigeminal nucleus did not show this similarity. It will be recalled that the substantia gelatinosa is the region of the spinal cord where small afferent fibers terminate, some of which have been implicated in mediating pain. In the trigeminal nerve there are fewer

unmyelinated fibers than in spinal nerves, but those present are said to pass into the caudal division of the trigeminal tract without bifurcating (Windle, 1926a, 1926b). In view of these anatomical and clinical findings, it is somewhat surprising to find that electrophysiological studies have failed to disclose a significant number of cells in the trigeminal nucleus which are activated by damaging stimuli (Gordon, Landgren and Seed 1961, Kruger and Michel 1962, Wall and Taub 1962, Darian-Smith, Phillips and Ryan 1963, Darian-Smith, Proctor and Ryan 1963, Eisenman, Landgren and Novin 1963). Almost all the cells encountered in the nucleus could be activated by weak mechanical stimulation of the skin of the face or of the mucous membranes of the oral cavity. A few cells have been seen by Eisenman et. al which responded specifically to damaging stimuli of both thermal and mechanical types, and Gordon et. al have described cells lying in the reticular formation on the medial border of the trigeminal nucleus which apparently respond in a similar fashion. Also, Wall and Taub have described cells in certain portions of the trigeminal nucleus which responded to weak mechanical stimuli, but which increased their frequency of discharge when the stimulus was made damaging. Investigators have also experienced difficulty in finding neurons in the trigeminal nuclei which respond to moderate temperature changes. Wall and Taub described cells which responded vigorously to both mild heating and gentle mechanical stimulation, but neither Gordon et. al. nor Eisenman, Landgren and Novin have reported cells of this type. The relative absence of cells responding to noxious stimuli and to moderate temperature changes is especially puzzling when it is recalled that studies of primary afferent fibers in the lingual (Hensel and Zotterman 1951c) and infraorbital branches (Hensel 1952) of the trigeminal nerve had defined what appeared to be specific thermal fibers, and smaller fibers which responded to damaging thermal and mechanical stimuli (Zotterman 1936, Iriuchijima and Zotterman 1960, 1961). Both anatomical and clinical studies have suggested that thermal and pain fibers turn toward the caudal part of the trigeminal nucleus, and it is difficult to escape the impression that for some reason there has been, in electrophysiological experiments, systematic exclusion of the cells to which these fibers project. This is not a remote possibility, because the cells are small in that part of the caudal trigeminal nucleus which resembles the substantia gelatinosa, and difficulties might be anticipated in recording from such cells.

## II. Post-synaptic elements in the spinal cord

Wall (1960), and Wall and Cronly-Dillon (1960) have studied the lumbosacral portion of the cat's spinal cord, and have in this region also found no cells which respond specifically to noxious or gentle thermal stimuli. These investigators did



isolate a type of neuron in the dorsal gray matter which could be well activated by gentle mechanical stimuli, and which also responded to noxious mechanical stimulation. In addition, these cells responded to non-noxious heating, although they were not particularly sensitive to this stimulus. Their behavior in response to thermal stimuli did not seem to correspond to that of the "specific" thermosensitive C fibers described by Hensel, Iggo and Witt (1960). The nature of the response of these cells to noxious heating was not discussed. The neurons were thought to lie in the dorsal horn deep to the substantia gelatinosa, and to send their axons into the ipsilateral dorsolateral funiculus. Apparently no recordings could be made from the cells of the substantia gelatinosa itself, which, as indicated above, are small.

### III. Post-synaptic elements in the dorsal column nuclei

In addition to recording from cells in the lumbosacral region of the spinal cord, Wall (1961) has also examined the responses of cells in the dorsal column nuclei, which are cell groups to which dorsal column fibers project. He found that these neurons responded well to gentle mechanical stimuli, and that in contrast to the cells described above in the dorsal horn of the spinal cord, they showed no further increase in discharge when the mechanical stimulus was made noxious. The reaction of units in the dorsal column nuclei to thermal stimuli was not studied. Perl, Whitlock and Gentry (1962) have investigated cells in the dorsal column nuclei while applying thermal and mechanical stimuli to the skin, though apparently they did not use noxious stimuli. It was found that post-synaptic neurons responded as if they were being influenced by only one type of cutaneous afferent fiber. For example, units were seen which responded to hair movement, with no indication of any further activation when the skin and hair were stimulated together. Like the "hair" receptor afferents studied in peripheral nerves, these cells did not respond to thermal stimuli, and the discharge was rapidly adapting. Other neurons behaved as if they were being influenced only by slowly adapting cutaneous receptors. They were not well activated by hair movement, gave a slowly adapting response when the skin itself was displaced, and responded with a phasic discharge when the skin was cooled. In addition to showing the remarkable specificity with which connections are made in the dorsal column nuclei, the work of Perl et. al. is important for two reasons:

1. Certain types of afferent responses, studied thus far only in peripheral nerves, have been shown to be mediated by the dorsal column system.
2. No cells were found in the dorsal column nuclei which responded with high sensitivity to



gentle thermal stimuli. A number of other studies have been made of the dorsal column nuclei, but they have been concerned only with responses to mechanical stimulation and are therefore not directly pertinent to the question of how different modalities of cutaneous sensation are experienced.

#### IV. Summary of post-synaptic responses

The behavior of post-synaptic elements in the spinal cord and brain stem can be summarized as follows: 1. No cells have been found in the spinal cord which respond specifically to noxious stimuli, and only a very few have been found in the trigeminal nucleus. 2. Cells which do respond specifically to noxious stimuli have been found in the reticular formation just medial to the trigeminal nucleus. 3. No cells have been found in the spinal cord which respond with high sensitivity to thermal stimuli. 4. Wall and Taub (1962) have described cells in the trigeminal nucleus which respond with high sensitivity to both gentle thermal and gentle mechanical stimuli, but Eisenman et. al. (1963) and Gordon et. al. (1961) have not reported units of this type. 5. Wall and Cronly-Dillon (1960) have described cells in the spinal cord which respond to both gentle and strong mechanical stimuli and also to heating. 6. Units in the dorsal column nuclei respond in a manner suggesting that they are driven in a highly specific way by mechanoreceptors associated with cutaneous myelinated fibers.

#### V. Mechanism for modality discrimination

It is evident that post-synaptic neurons responding specifically to non-noxious mechanical stimuli have been found in rather large numbers in the central nervous system. Post-synaptic units responding to gentle thermal stimuli have been seen much less often (not at all in the spinal cord), and those found did not respond exclusively to such stimuli. This lack of specificity contrasts with the quite specific behavior of thermally sensitive primary afferent fibers. The absence of units in the spinal cord and trigeminal nucleus responding specifically to noxious stimuli is also striking. Thus it is clear that some post-synaptic units respond in a specific fashion to cutaneous stimuli, and others respond to more than one kind of cutaneous stimulation. Evidence appears to exist both for information transfer along anatomically distinct non-convergent pathways, and for information transfer in convergent systems where specific patterns of discharge presumably convey information regarding the type of stimulation occurring. Another possibility is that some or all of the convergent systems are not involved in the transfer of sensory information, but rather in motor reflex or alerting

functions. Wall and Taub (1962), and Kruger and Michel (1962) have interpreted the absence of units responding specifically to noxious stimuli to mean that pain is felt as the result of a particular pattern of impulses in neurons which can also be activated by other stimuli, though the precise nature of this pattern has not been indicated. It is possible that this explanation is correct, but two facts must be remembered in evaluating it. 1. Specific units highly sensitive to thermal stimuli have been as elusive as specific nociceptive units. Either the thermal units have been missed, or the common carrier theory should be extended to include them also. 2. The small cells in the gelatinosa of the spinal cord and trigeminal nucleus, considered at least in the spinal cord to be the sole terminus of small afferent fibers, have so far resisted analysis by electrophysiological techniques. Finally, it should be noted that in determining the role of convergent systems it would be of great interest to know whether stimuli related to different modalities do in fact set up different patterns of activity.

In the experiments to be described below recordings have been obtained from single units which respond to both thermal and mechanical stimuli. These units were located in the lateral columns and seem comparable to those studied by Wall and Cronly-Dillon. It has therefore been possible to determine whether the pattern of discharge in a particular unit varies in some characteristic way with the kind of cutaneous stimulation applied. No such characteristic differences have been seen. In addition, it has been possible to record from primary afferent fibers in the dorsal columns while subjecting the skin to a variety of relatively well defined stimuli, and compare the responses of these units with those studied in the lateral columns.

## Methods

Methods employed in carrying out experiments like those of the present study fall into various categories: There are procedures concerned with preparation of the animal, and evaluation of the animals condition; those related to recording the activity of individual nerve fibers, and determining the site from which recordings have been obtained; procedures used in applying various stimuli to the skin; and finally those required in the presentation and analysis of the data. Each of these will be considered in turn.

### I. Preparation of the animal

Unanesthetized, high spinal cats were employed in all experiments. Under initial ether anesthesia the trachea was cannulated and both common carotid arteries were ligated. A cannula was inserted into one common carotid artery proximal to the tie, so that the blood pressure could be measured. This cannula led to a mercury manometer. The spinal cord was sectioned at the level of the atlanto-occipital junction, and the vertebral arteries clamped. At this time artificial ventilation was begun and the anesthetic discontinued. Actual recording did not start until at least 2 hours after removal of the anesthetic. The lower lumbar and sacral regions of the spinal cord were exposed by laminectomy and covered with mineral oil which had been equilibrated with a 95% O<sub>2</sub> - 5% CO<sub>2</sub> gas mixture. The mineral oil was held in a pool, the walls of which were formed by tying up flaps of skin available from the dissection. Both oil pool and rectal temperatures were held between 36 and 39°C with the aid of infra-red lamps.

In any experiment in which recording is attempted from single axons, it is important that no gross movements of the animal occur during the recording period. Stabilization of the animal was achieved as follows: The hips were supported by pins that pressed against the illia, the spine was supported by clamping the dorsal spinous process just rostral to the exposed spinal cord, and a pair of clamps were placed so that they pressed against the sides of the vertebral column. The animals were paralysed with Flaxedil (gallamine tri-ethiodide), and, when necessary, a unilateral pneumothorax was performed.

### II. Evaluation of Animal's Condition

It is important that the preparation not undergo significantly more deterioration than that unavoidably caused by the dissection procedures. The chief criteria used in evaluating the condition of the animal were the blood

pressure and the magnitude of exteroceptive spinal reflexes.

The mean arterial blood pressure is considerably higher in the intact anesthetized cat than in the high spinal animal, and the blood pressure generally fell from over 100 mm Hg to 70-80 mm Hg as a result of the spinal transection. It was not unusual for the blood pressure to fall even further in the course of the experiment. The acceptable lower limit for the blood pressure was considered to be 60-65 mm Hg, because it was at approximately this value that withdrawal reflexes to pinching the toes could no longer be obtained. If the blood pressure fell below 60 mm Hg the experiment was discontinued, though it is admitted that the presence or absence of exteroceptive reflexes constitutes a crude and perhaps irrelevant assessment of the capacity of the spinal cord to transmit sensory information. The blood pressure during most of the experiments was 70-80 mm Hg.

### III. Method of Recording

Steel microelectrodes were used to record the activity of single axons in the white matter of the spinal cord. The animal was grounded through the head holder and the action potentials recorded against ground. The electrodes were prepared according to the method of Green (1958), in which steel insect pins are sharpened electrolytically in concentrated HCl, and then coated with an insulating lacquer which leaves only the tip bare. The diameter of the electrodes at the tip was approximately one micron, and an attempt was made to keep the taper gradual. Action potentials recorded with such electrodes ranged in size from 200 microvolts to about 20 mv and had the same configuration regardless of size. The potentials were diphasic, with a large positive phase followed by a small negative one. The action potentials shown in Figure 1 are typical, the negative phase being so small that it can hardly be distinguished. In the present study no attention was given to the shape of the recorded action potentials, since the only concern was with whether or not a discharge had occurred.

From the microelectrode the recorded activity was led into a cathode follower, and thence through a high pass filter into a Tektronix 502 dual beam oscilloscope. The oscilloscope both amplified and displayed the activity, and when desired the activity could be photographed with a Grass kymograph camera. The activity was led onto magnetic tape, from the final stage of the oscilloscope vertical amplifiers, through a clipping circuit which provided a lower bound. Any noise present in the original record could be set below this lower bound, and action potentials rising above the bound would appear without noise at the output of the clipping circuit. These action potentials were then amplified and used to



Fig. 1. The upper trace shows activity initiated in a dorsal column primary afferent fiber by hair movement. On the lower trace are time marks at intervals of 100 msec. Upward deflections are positive going.

trigger a pulse generator (Textronix 161) that provided standard sized pulses which were recorded onto magnetic tape through one channel of a Uher stereophonic tape recorder. Time marks at a frequency of 2000/sec were recorded onto the second tape recorder channel. The beginning or end of a stimulus was indicated by manually closing a switch which caused an unusually large potential to appear on the tape channel recording the nerve impulses. Stimulus indication by this method is not particularly exact, the error being about  $\pm 0.5$  sec.

An important limitation of microelectrode recording as employed in this study is the tendency for this method to select large fibers. That such a selection actually occurred in these experiments could be shown in the following way. While recording from a single primary afferent fiber in the dorsal columns the receptive field of the unit was stimulated electrically through an electrode inserted into the skin. Monopolar stimulation against ground was employed, using rectangular pulses with a duration of 40 microseconds, which could be given at any desired frequency. Usually the responses to such stimulation were photographed from the oscilloscope onto film which was moving at high speed. A time marker with a frequency of 2000/sec. was photographed simultaneously. It was thus possible to determine the latency of the response, and by measuring the length of the afferent pathway it was possible to calculate the approximate conduction velocity of the fiber being studied. It was found that all the fibers so measured, from which stable recordings were obtained, had peripheral conduction velocities in excess of 50 m/sec. Most of the values fell between 60 m/sec. and 70 m/sec. Conduction velocities of this magnitude place the fibers studied among the largest in cutaneous nerves (Hunt and McIntyre 1960b). It seems reasonable to assume that recording conditions in the dorsal and lateral columns would be similar and that selection of large fibers would occur in the lateral columns also.

#### IV. Stimulation Procedures

Once a single unit had been isolated with the microelectrode it was possible to test its responsiveness to different kinds of natural stimulation. The stimuli used have been only roughly quantitative, since the principal concern was to test the sensitivity of single fibers to a variety of stimuli. Mechanical and thermal stimuli have been used most often, but pressure was sometimes applied to deep structures, in a few cases after removal of the skin. Joint movement was also employed, the joint being rotated manually in a not particularly selective or quantitative fashion. In general, there was no attempt to locate by dissection the actual site of the receptors responsible for the discharges produced by deep pressure or joint rotation.

#### A. Mechanical stimulation of skin

For estimating the sensitivity of a particular unit to mechanical stimulation, a graded series of von Frey hairs (cat vibrissae) were used. These were calibrated in milligrams on an equal arm balance, the hair being given a value equal to the weight that it was able to support when slightly bent. Another estimate of the sensitivity of a unit to mechanical stimulation was obtained by applying spring clips to the skin. These were also graded in strength, and will be described subsequently in terms of the sensations they evoked in man - "mild", "firm", and "noxious". By observing the frequency of discharge as a function of time after the application of such a clip, it was possible to determine the rate of adaptation of the response. A camel's hair brush was used for moving hairs without touching the skin. To insure that this stimulator engaged only the hairs, the area being tested was generally unclipped, so that the skin could be avoided by touching just the tips of the hairs. The usual procedure was to first test the responsiveness of the unit to hair movement, and then to clip or depilate the responsive area for more precise definition of the dimensions of the receptive field.

A diffuse current of air was a stimulator which seemed to be effective mainly when hair sensitivity (as demonstrated with the hair brush) was present. This was especially so when the air was directed onto the unclipped receptive field. The air stimulator could be given either as a continuous blast, or as puffs. The latter were produced by allowing the air to pass through holes in a wheel which could be rotated at varying speeds (Adrian, Cattell and Hoagland 1931), and gave some indication of the frequency following capacities of the units to this kind of stimulation.

The methods of mechanical stimulation discussed thus far could be shown to activate units with receptive fields in the skin much more effectively than units with subcutaneous receptive fields. The latter could be distinguished from the former because subcutaneous units were best activated by stimuli that resulted in pressure on deeper tissues, and were not appreciably activated when the skin was lifted from underlying tissues and compressed, a procedure which effectively activated cutaneous units. The methods of mechanical stimulation which are to be considered next were capable of activating both cutaneous and deep units.

The moving coil of a vibration generator (Goodmans V47) provided another stimulator, the frequency of which could be varied. A light, hollow, plastic rod with a rounded tip was attached to the coil, and this rod placed on the receptive field. The vibration generator was activated by rectangular pulses, amplified by a transistorized power amplifier designed by L. Eisenberg of the Rockefeller Institute. The displacement of the coil was abrupt at all frequencies with this type of input. The vibration generator had a resonant frequency of about 70 cycles per second, so that the amplitude of the vibration fell off sharply as one went to lower or higher frequencies. This decline could be alleviated to some extent by increasing the width of the actuating pulse.

In order to give repeated mechanical stimuli which were roughly equivalent, a syringe was used which was filled with air at constant pressure (Hunt and McIntyre 1960a, 1960B). A glass rod was attached to the plunger of the syringe. On this rod could be mounted lucite stimulators of varying size, those usually employed being either 3 mm in diameter or 1 mm in diameter. Neither of these caused pain in humans with the syringe air pressure used. Also, a sharply pointed lucite tip could be attached, and this was distinctly painful when applied to human skin. By attaching first one stimulator and then another, and using each for stimulation of the same site with a constant air pressure in the syringe, it was possible to achieve fairly controlled noxious and non-noxious stimulation of a particular region. The syringe was generally held by hand for such studies. Sometimes a steel needle was inserted into the skin as an additional noxious stimulus.

Also, it was of interest to test the units with stimulators that differed in texture. For this purpose four identical polished lucite discs were used, about one inch in diameter and one half inch thick. Around the circumference of three of these discs was glued sandpaper, a different grade of sandpaper being applied to each of the three. The stimulators were drawn across the receptive region by hand, the speed being varied as desired. Human subjects had no difficulty in distinguishing between these stimulators on the basis of textural differences alone.

#### B. Thermal stimulation

Three methods were used to change the temperature of the skin. Heating was accomplished with radiant energy and by circulating water which had been raised to the desired temperature, through a metal thermode placed on the



dampened receptive field. Cooling was accomplished with the thermode, and by spraying ethyl chloride onto the receptive field. Each of these procedures will be discussed in turn.

Radiant heat was obtained from a hot glass rod held next to the skin but not touching it. Just previously the rod had been heated in an oxygen-gas flame. The temperature of the skin was not measured when it was heated in this way, except in a few cases after recording had been terminated at the end of an experiment, and in one spinal animal set up specifically for this purpose. The subcutaneous temperature was measured in these particular experiments, using a thermistor inserted just under the skin. It was found that subcutaneous temperatures rose from initial values of 37°C or 38°C to 45°C or 50°C during application of radiant heat. If the period of warming was prolonged, an obvious blistering of the skin occurred. Thus it can be said that if a unit fails to respond to radiant heating as here applied, then strong heating is inadequate to excite it. However, if the unit responds, it is not possible to know the threshold of the response using this method.

When skin temperatures were raised using the thermode, the temperature of the surface of the skin was routinely measured while the neural response to heating was being recorded. The temperatures were measured with a thermistor that was attached to the bottom of the thermode, but insulated from it with epoxy resin. The thermistor constituted one arm of a Wheatstone bridge, the output of which could be displayed on the oscilloscope and photographed, or recorded on paper (a Brush Mark II DC recorder was used). In this way a continuous record of temperature was obtained. This record could be compared with the record of action potentials on magnetic tape by insuring that the stimulus marker pulses on the tape record caused a transient deflection of the temperature trace. Using the thermode, the temperature of the skin could be raised to any desired level by circulating water heated to the appropriate temperature.

When the thermode was used for cooling the skin, the method for recording the skin temperature was the same as that employed with thermode heating. Here too the temperature of the skin could be brought to any desired level by circulating fluid which had been appropriately cooled. Water was usually employed, though when especially strong cooling was desired, acetone, which had been cooled with dry ice, was circulated. When ethyl chloride was used for cooling the skin, the

subcutaneous temperature was measured as in the experiments with radiant heating. In addition, attempts were made to measure the temperature of the skin surface when ethyl chloride was used as a stimulus. This was done by enfolding a thermistor in a groove of skin at various times after spraying the skin surface with ethyl chloride. It was found that the duration and rate of cooling were dependent on whether the skin had been clipped. The temperature fell for a longer time but less rapidly if the skin was covered with hair, because the ethyl chloride evaporated more slowly. Subcutaneous temperatures fell from initial values of 37°C or 38°C to around 15°C when the application was to unclipped skin, and from the same initial values to around 20°C when applied to skin which had been clipped. The temperature of the surface fell to near 10°C when clipped skin was sprayed. It should be noted that there is a complication when ethyl chloride is used to cool mechano-sensitive receptors because the application of ethyl chloride causes a transient mechanical disturbance. However the major part of the cooling occurs after this disturbance is over, and the usual procedure was to examine the response only after the end of the period of application. The comments made with regard to warming with radiant heat apply equally to ethyl chloride cooling. If there is no response to spraying ethyl chloride onto the receptive field than it is likely that the unit does not respond to strong cooling. If there is a response, nothing can be said about its threshold.

In summary, it can be said that when heating and cooling were performed with the thermode it was possible to control quite well both the rate of cooling, (by regulating the rate at which the fluid entered the thermode) and the final temperature reached. Also, the temperature of the skin surface could be measured continuously during such experiments. When warming with radiant heat, and when cooling with ethyl chloride, neither rate of temperature change nor final temperature were well regulated. Hence, the non-thermode methods for changing the skin temperature are mainly of value in indicating whether or not a thermal response can be obtained.

#### IV. Histological Verification of Recording Site

The microelectrode could be placed under visual control into either the dorsal columns or the lateral white matter of the spinal cord, depending on which type of unit was under study. The fine movements of the electrode were controlled by an oil filled microdrive. The approximate depth at which a particular unit was recorded could be determined by examining the scale on the microdrive, but it was important to know more precisely the point within the spinal cord from which a par-

ticular recording had been made. Such information was obtained by making a lesion in the white matter at the site of the recording microelectrode tip, after the responses of a unit had been studied sufficiently to characterize it. This lesion was produced by passing anodal or cathodal current through the microelectrode (usually one microampere for one minute) using a remote electrode to complete the circuit. At the end of the experiment, the segment of the spinal cord which contained the lesion was removed and fixed in formalin. After dehydration through graded alcohols, the tissue was embedded in paraffin, serially sectioned at 20 microns, and stained with either cresyl violet or thionin. Better visualization of the white matter could be obtained if the sections were counter-stained with crisoidin y, and this was done in all later experiments. When measured on transverse sections of the spinal cord prepared as outlined above, the lesions had diameters of 50 microns to 200 microns, the usual size being about 150 microns. The lesions were symmetrical (oval or circular) and it was assumed that the electrode tip lay somewhere near the center. A lesion of 150 microns in diameter, while too large for very precise localization, can nevertheless serve to indicate the region of the spinal cord in which a particular recording was made, and has the advantage of being easily visible, and not readily confused with preparation artificats.

#### V. Data Display and Analysis

The main concern in the present experiments was whether a discharge occurred in response to a particular kind of stimulation, and with the information that such a discharge might convey regarding the modality and strength of the stimulus. To obtain such information, two general procedures have been used. In the first procedure, the output of the tape recorder channel onto which the action potentials had been recorded was amplified, and fed into a Hewlett Packard counter, which was gated to count impulses over an interval of 190 msec. The counter had a reset time of just under 10 msec. The tape was played back at half the recording speed so that while 190 msec. elapsed in real time, the tape played back the events that occurred during 95 msec. The analog output of the counter, which represented the number of impulses occurring in a 95 msec. interval, was graphed using a Brush Mark II DC recorder. For this method to be accurate, the tape recorder must play back at exactly one half the speed at which it records. The large potentials which indicated the beginning or end of a stimulus, in addition to being unavoidably counted as action potentials, could selectively activate a Tektronix 161 pulse generator, the output of which caused a suitable deflection on a marker channel of the DC recorder.

In the second method of data display, both time marks and action potentials from the tape recorder were amplified and led into a Control Data 160A computer made available through the courtesy of Dr. Hartline. The computer had been programmed to graph successively the magnitude of each interspike interval on the ordinate against an arbitrary and equal displacement on the abscissa. This made it possible to see individual interspike intervals, and the sequence in which they occurred. Thus the detailed composition of the 95 msec. blocks of time already graphed with the DC recorder could be visualized, especially with regard to maximum frequency of firing and overall regularity of the discharge. The computer was also programmed to make average frequency plots against time, and in this case it was possible to vary at will the interval over which the averaging was done.

The computer average frequency plots were made in the following way:

1. The number of complete interspike intervals occurring during the averaging interval was determined.
2. When an interspike interval was partially included in the averaging interval, that fraction of the interspike interval which occurred during the averaging period was calculated and added to the number of complete interspike intervals already determined.
3. The sum of the complete and partial interspike intervals occurring during the averaging period was plotted against time.

Typically the averaging intervals chosen were 2 sec., 0.5. sec., and 20 msec. Using the longer averaging intervals it was possible to examine the overall character of the activity; with the 20 msec. averaging interval it was possible to make a more detailed analysis of the pattern of the discharge in time.

Interval distribution histograms were also made. This was done by taking successively each of the interspike intervals that occurred in a particular block of time (five or ten seconds for example), and determining the duration of those intervals. The number of intervals with durations that fell within a particular range (5 msec. to 6 msec. or 200 msec. to 250 msec. for example) were then plotted on a graph where the ordinate represented the number of intervals in a particular size range and the abscissa showed the time limits within which the interspike intervals fell. Fractional values appear on the ordinate in some cases because of the way the computer was programmed. In the present study, interspike intervals have been put into categories 1 msec. long (3 msec. to 4 msec., 4 msec. to 5 msec., etc.) out to 200 msec., and then into categories 50 msec. long (200 msec. to 250 msec., 250 msec. to 300 msec., etc.) out to 1000 msec. By examining such interval distribution histograms it is possible

to estimate the degree of irregularity in the discharge, and to determine the actual durations of the intervals represented. When it was desired to compare two separate responses, the histograms were always prepared so that the total histogram areas were the same in both cases. This allows a direct comparison of the relative number of intervals in a particular size category on the basis of the height of the histogram columns. The disadvantage of the interval distribution method of data representation is that the intervals are taken out of their proper sequence in time. Thus it is possible to imagine two separate discharges which have similar interval distribution histograms, but which differ considerably in pattern of discharge and degree of regularity. For this reason it was thought desirable to plot the activity in a way which preserved the sequence of events in time. To do this the first interval in a train of action potentials was taken into the computer, and from it was subtracted the next interval in the train. This difference was plotted against the magnitude of the second interval. Then the third interval was subtracted from the second, and the difference again plotted. This procedure was continued until the entire discharge had been analysed. The graph which results is called an interval difference plot. It can be seen that if the discharge is regular the differences between successive intervals will be small, while in the case of irregular activity the differences will be greater. By adding up the absolute values of the differences between all the successive intervals in a particular discharge it is possible to arrive at a quantitative expression for the degree of regularity displayed by that discharge.

## Results

### I. General Comments

The data to be discussed will be divided into two parts; the first will deal with activity recorded from the dorsal columns, the second with activity recorded from the lateral funiculus. As an aid in this discussion, it is useful to imagine that the spinal cord is made up of the several different areas which are shown in Figure 2. Reference to this figure will also indicate the regions of the spinal cord from which recordings have been made. The dorsal columns are the dorsally situated tracts bounded ventrolaterally by the dorsal root entry zone and the dorsal horns of the spinal gray matter. These columns are a bilateral structure, the right and left halves being separated by the dorsal median septum. All recording has been done in the left dorsal column, and most of the units to be discussed were recorded rather superficially. This is because as the electrode was inserted deeper into the white matter, units activated by proprioceptive stimuli became so prominent that they obscured the activity of any units which might have been influenced by cutaneous stimulation. Thus the more ventral portions of the dorsal columns have not been explored for the presence of units responding to cutaneous stimuli, and it is possible that fibers could be found in this region which have properties differing from those to be described below. No recordings have been made from the ventral funiculus, which is considered here to include that region of the white matter which lies between the anterior median fissure and the most lateral filaments of the ventral roots. The remaining white matter constitutes the lateral funiculus. This region includes all the fibers lying between the ventral and dorsal roots in the lateral part of the spinal cord. Recordings have been made from various parts of the lateral funiculus, and to describe better the areas where recording has been done it is convenient to divide the lateral funiculus into a dorsal and ventral part. The dorsal part of the lateral funiculus is that part which lies above a horizontal line drawn from one side of the spinal cord to the other through the central canal. The ventral part of the lateral funiculus lies below this line. Most of the units to be discussed were located in the dorsal part of the lateral funiculus.

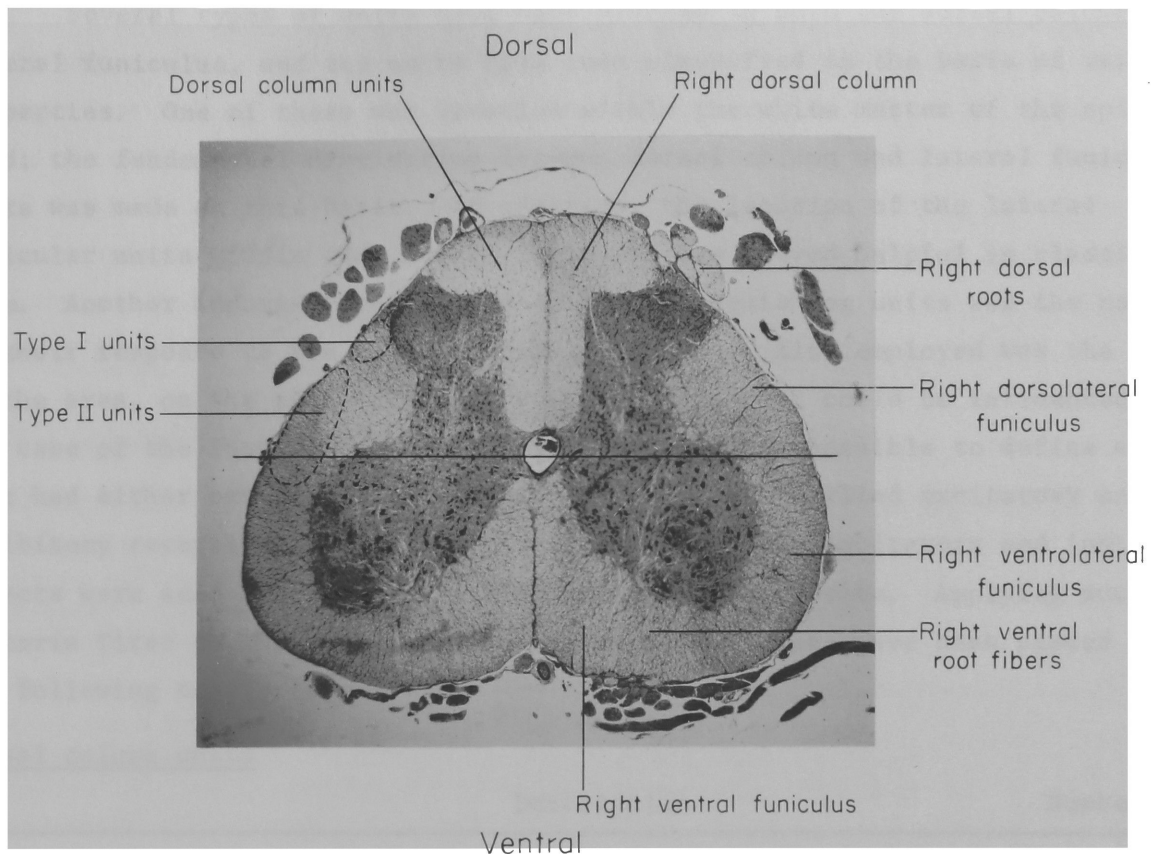


Fig. 2. Cross section of the lower lumbar spinal cord of the cat, stained with cresyl violet and crisoidin y. Dorsal and ventral halves of the spinal cord are demarcated by a horizontal line passing through the central canal. The various parts of the white matter are indicated on the right. On the left are indicated the regions in which the different types of units were recorded.

Several types of units have been studied in both the dorsal columns and lateral funiculus, and the units have been classified on the basis of various properties. One of these was location within the white matter of the spinal cord; the fundamental distinction between dorsal column and lateral funicular units was made on this basis. In addition, the location of the lateral funicular units within the lateral funiculus has proved helpful in classifying them. Another important property used in distinguishing units was the nature of their response to the various stimuli applied. Also employed was the location of the area, on the skin surface, from which the unit could be influenced. In the case of the lateral funicular units it was often possible to define areas that had either excitatory or inhibitory influences (called excitatory and inhibitory receptive fields) and, in some cases, both excitatory and inhibitory effects were seen to result from stimulating the same site. Applying such criteria first to the dorsal column units, most of them have been placed into the following categories.

Dorsal column units

Description	Number
Best activated by hair movement, rapidly adapting. Hereafter called "hair" unit.	34
Best activated by touching skin, slowly adapting, located in glabrous foot pad skin and hairy regions. Hereafter called "tonic touch" unit.	14
Best activated by touching skin, rapidly adapting, located in glabrous foot-pad skin. Hereafter called "phasid pad" unit.	5
Best activated by pressing on subcutaneous tissues or by joint movement, slowly adapting.	10

The last group consists of units which are not of any particular relevance for the problem of how cutaneous modalities are discriminated, but which are included because their pattern of discharge presents an interesting contrast to that of units activated from skin. Fibers have been encountered which can not be placed into any of the categories outlined above, but they have been seen too infrequently to justify serious consideration at this time.



It can be seen that the above classification is based predominantly on the nature of responses to effective stimuli. Nothing can be said about the detailed structure of the receptors, and it is possible that receptors with diverse morphology are being included within a single category. Another point which it may be well to emphasize again is that the recording technique employed selects the larger fibers, systematically excluding an entire range of smaller fiber sizes.

Lateral funicular units have been classified as follows:

Lateral funicular units

Description	Number
Situating just beneath dorsal root entry zone (see Fig. 2), discharge irregular with short interspike intervals well represented, best activated by gentle mechanical stimulation of the skin. Hereafter called type I.	17
Situating more ventrally than type I in the dorsal part of the lateral funiculus, discharge fairly regular with no short interspike intervals, activated by stimulating both skin and subcutaneous structures; hereafter called type II.	8

The fibers which have been studied thus far in the lateral funiculus show rather complex behavior, and units have been found which do not clearly fall into the above categories. Again, these are too few in number to justify discussion. In fact, of the above categories, only the first is very clearly defined, and the type II category may include units which are functionally quite diverse. Again it must be emphasized that the recording technique selects the larger fibers.

Before going on to a more detailed discussion and comparison of the various categories of units described above, the following general remarks can be made. All cutaneous units in the dorsal columns have been found to respond best to gentle mechanical stimuli. There is either no response to thermal stimuli, or when such a response does occur, its frequency is low compared to the highest frequencies that can be obtained with appropriate mechanical stimulation. Strong and damaging stimuli, either mechanical or thermal, cause a disappearance of evoked activity in dorsal column units. On the other hand, all units in the lateral funiculus have been found to respond to both thermal and mechanical stimuli with an appreciable discharge. Thus the lateral funicular units are all activated by stimuli related to more than one modality of cutaneous

sensation (polymodal). In addition, evoked activity in lateral funicular units is not readily depressed by strong thermal and mechanical stimuli.

## II. Dorsal Column Units

### A. "Hair" units

#### Properties of "hair" units - gentle mechanical stimulation

Of the units in the dorsal columns activated by cutaneous stimuli, the "hair" unit has been most frequently encountered. If one moves a hair brush across the unclipped receptive field of such a unit, touching only the hairs, there is a burst of activity each time the hairs are displaced. This is illustrated in Fig. 1 and Fig. 3A. Fig. 1 shows activity evoked by hair movement which has been displayed on the oscilloscope and photographed. The graph in Fig. 3A shows, for another unit responding to the same stimulus, frequency of discharge plotted on the ordinate with time on the abscissa. In calculating the frequency, the discharge has been averaged over periods of 20 msec., and so some of the detailed structure of the response can be seen. It has been a general finding that "hair" units do not show spontaneous activity, and by examining Fig. 3A, it can be seen that activity is restricted to the time of stimulation. "Hair" units are characterized by the fact that stimulating both skin and hair of the unclipped receptive field together does not increase the discharge beyond that which is obtained if hair alone is stimulated. Another aspect of the response of these units is that the frequency of the discharge is roughly proportional to the rate at which the stimulator moves across the receptive field. A greater proportion of short intervals occurs in the discharge if the velocity of the stimulator is increased. This can be seen by comparing the frequency plot in Fig. 3A with that in Fig. 3B. Fig. 3A shows the response which occurred when the hair brush was drawn fairly slowly across the field; in Fig. 3B the brush was moved more rapidly. The frequency of stroking was also higher in Fig. 3B, so the overall baseline is elevated. In both cases only the hairs were engaged. This point is further illustrated in Figures 3C and 3D, which show interval distribution histograms of the responses plotted in Figures 3A and 3B respectively. It can be seen that many short intervals occurred even when the hair brush was moving slowly across the receptive field. It is characteristic of these units that even a slow, gentle stimulus causes a discharge in which short intervals are present. However, a considerably larger proportion of the intervals are of short duration if the stimulator is moved rapidly across the field. Thus "hair" units may be said to show "velocity sensitivity".

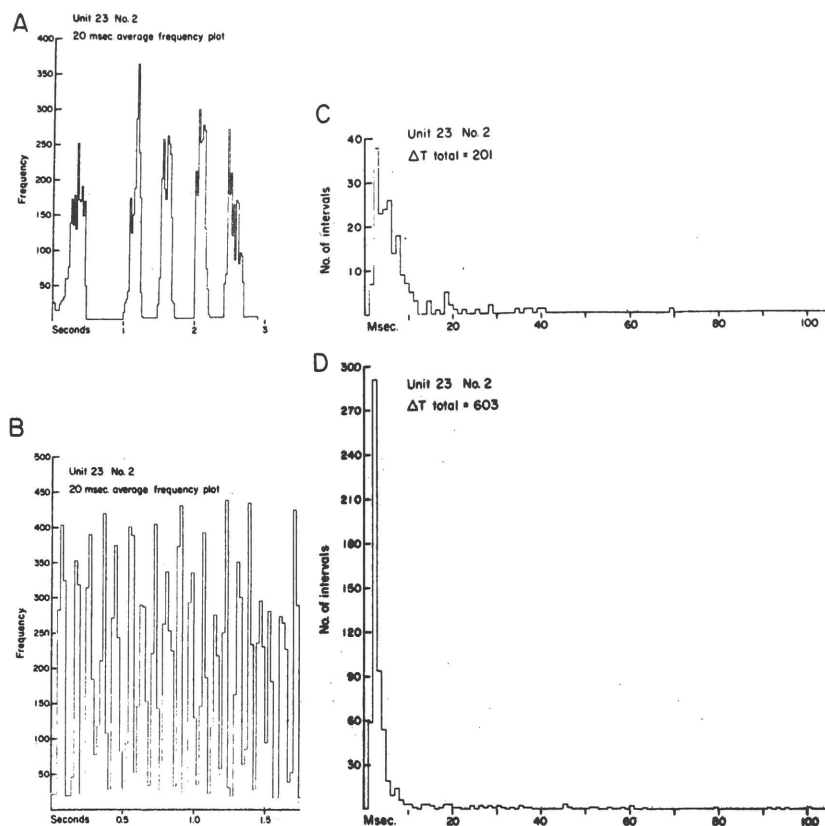


Fig. 3. Response of a dorsal column "hair" unit to repeated stroking of the receptive field with a hair brush, the stimulator engaging only the hairs of the area. There is a separate burst of activity each time the stimulator crosses the receptive field. Fig. 3A shows a 20 msec. average frequency plot of the discharge that occurs when the stimulator is moved relatively slowly across the receptive field. Fig. 3B shows a similar plot of the activity which results when the stimulator is moved more rapidly across the receptive field. The rate of stimulation is also increased in Fig. 3B so that the overall baseline is elevated. Figures 3C and 3D are interval distribution histograms of the data plotted in figures 3A and 3B respectively. The histogram area is the same in both 3C and 3D, so that a direct comparison of the relative number of intervals in a particular size category can be made on the basis of the height of the appropriate histogram column. This procedure has been followed in all cases where it is desired to compare the interval distribution histograms of two different responses. In this case, though the unit is well activated by both slow and rapid movement of the hairs covering the receptive field, rapid movement is the more effective stimulus, and the unit can be said to show velocity sensitivity.

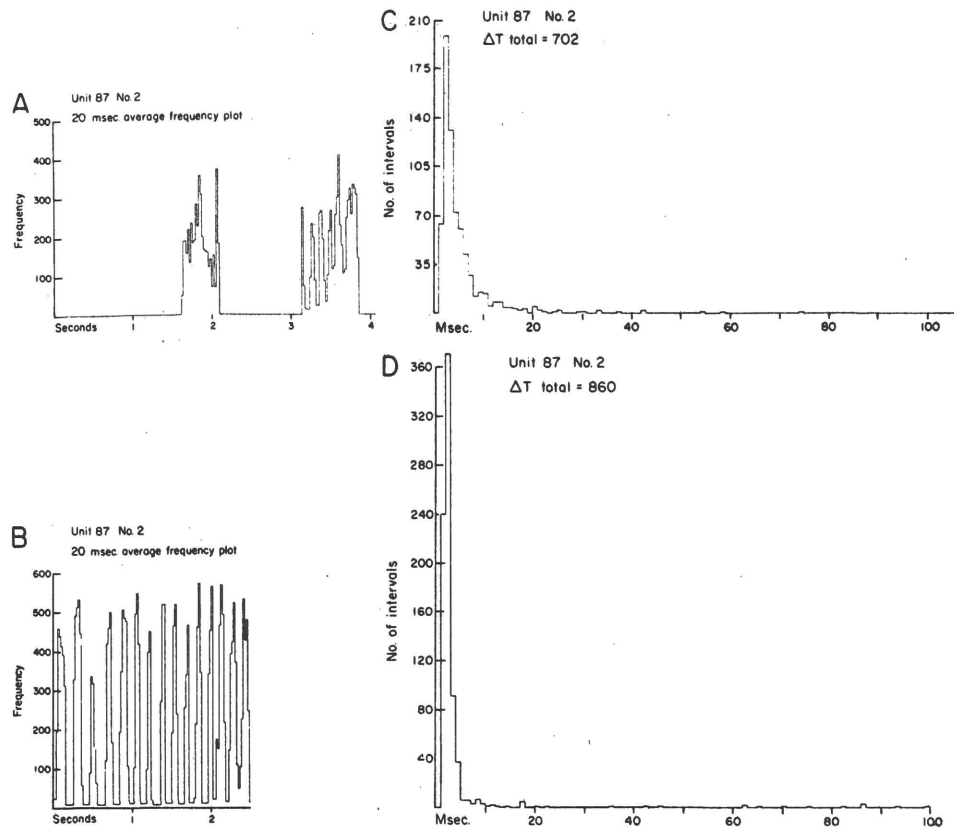


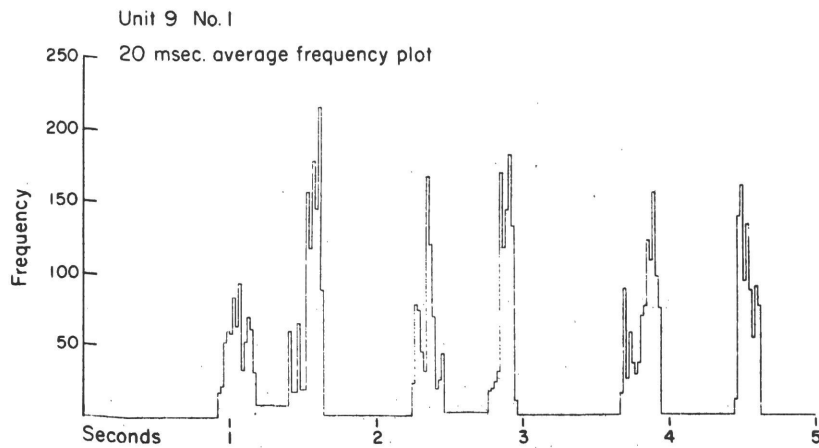
Fig. 4. Discharge in a dorsal column "hair" unit in response to stroking the deplaitated receptive field with the finger. A separate burst of activity occurs each time the finger moves over the receptive field. Figures 4A and 4B are 20 msec. average frequency plots of the response to slow and rapid stroking respectively. Figures 4C and 4D are interval distribution histograms of the responses to these stimuli, fig. 4C showing the response to slow stroking, fig. 4D to rapid stroking. It can be seen that the unit is well activated by these gentle stimuli, and that the higher the velocity of the stimulator the more effective the activation.

If the receptive field of the "hair" unit is clipped or depilated, a vigorous response can still be obtained by stimulating the skin directly. The hair brush applied to the skin is not especially effective, somewhat stronger stimulation being optimal. Gentle rubbing of the skin with the finger is a good stimulus, as shown in Fig. 4. Figures 4A and 4B show frequency plots with a 20 msec. averaging interval of the activity resulting from slower and more rapid stroking of the receptive fields respectively, and Figures 4C and 4D show interval distribution histograms of the same responses. Again, velocity sensitivity is evident.

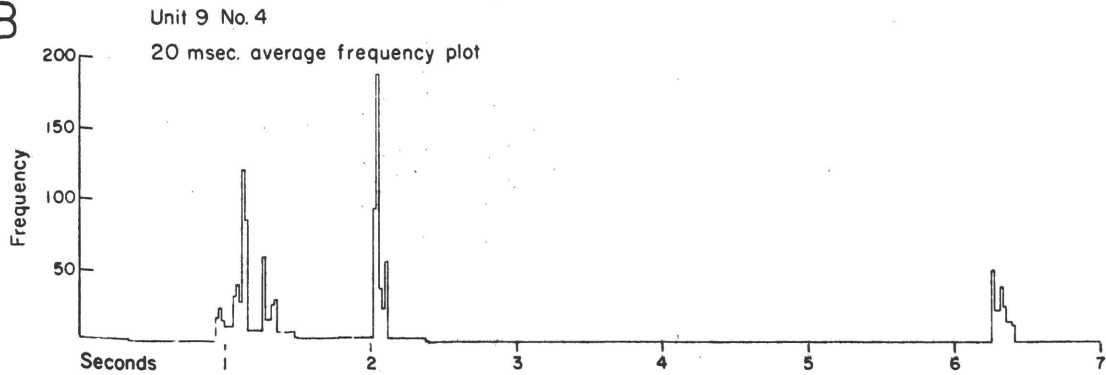
Another prominent feature of "hair" unit behavior is rapid rate of adaptation. This is illustrated in Figure 5. Fig. 5A shows the response of a unit to moving the hairs of the receptive field several times with a hair brush. 5B shows the response which resulted when the "firm" clip was applied to the receptive field. The clip caused a reasonably steady displacement of both skin and hair. It can be seen that the response occurred only while the skin and hair were being moved as the clip was put on and removed. This has been a general finding; the receptors respond only during movement of the skin and hair. Fig. 5C shows the response of the same hair unit to application of the noxious clip; this response will be discussed later.

Several other mechanical stimulators have been used to activate "hair units". One of the most effective of these was a current of air. The greatest number of short intervals was obtained when the air current was interrupted, so that with each puff of air the hairs were rapidly bent. This is illustrated in Figure 6A. A response could also be obtained when the current of air was continuous, and the discharge, after declining somewhat at first, was maintained as long as the current of air continued. This is shown in Fig. 6B. If the receptive field was clipped or depilated the response to air currents was greatly reduced, though some discharge remained. Each puff of air now gave one or two nerve impulses rather than the burst seen when the field was unclipped. It is interesting that "hair" units could be driven to quite high frequencies by giving repetitive puffs of air to the clipped field. The highest repetition rate that could be achieved with the apparatus available was about 230/sec. and the units regularly followed at this frequency, giving one discharge for each air puff. If the receptive field was unclipped, such high frequency following was not obtained, presumably due to the fact that the intact hair added sufficient mass to render an adequate mechanical following of the stimulus difficult.

A



B



C

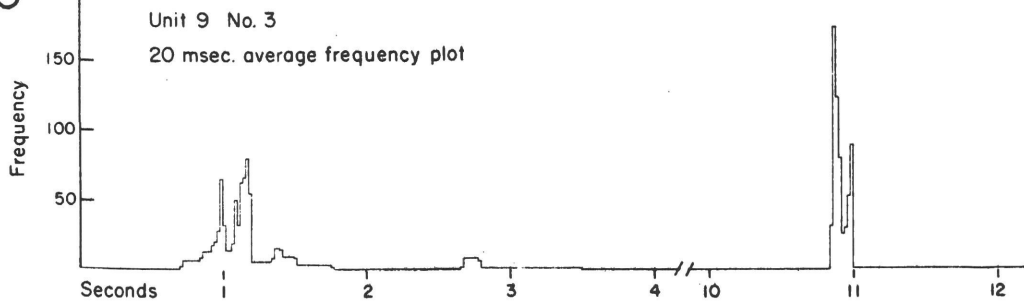


Fig. 5. Fig. 5A shows the response of a "hair" unit to repeated displacement of the hairs of the receptive field with a hair brush. In fig. 5B the "firm" clip is applied to the receptive field of this same unit, and removed a few seconds later. The unit responds only during the movement of the skin and hair caused by application and removal of the clip, the periods of activity thus indicating when the clip was applied and removed. In fig 5C the "noxious" clip is applied and removed somewhat later.

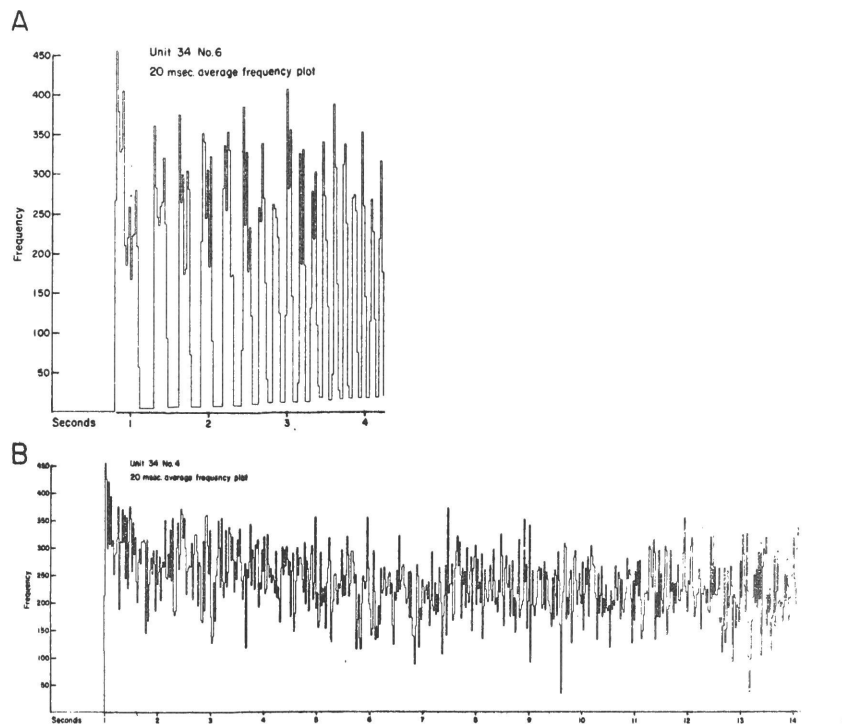


Fig. 6. Fig. 6A shows the response of a "hair" unit to an interrupted jet of air which is being applied to the unclipped receptive field at a progressively increasing rate. Fig. 6B shows the response of this same unit to a continuous current of air. These gentle stimuli activate the unit very effectively.

Another high velocity mechanical stimulus was provided by the moving coil of a Goodmans V47 vibration generator. The vibration generator was driven by pulses 0.5 msec. to 1 msec. in duration, and could produce repetitive mechanical displacements at frequencies in excess of 500/sec. Because the resonant frequency of the coil was approximately 70/sec., the amplitude of the coil movement was considerably reduced at frequencies above 100/sec. In spite of this, it was possible to obtain following from "hair" units at frequencies up to 500/sec. At this frequency the receptor only followed for a short time (200 msec. to 300 msec. maximum), as can be seen in Fig. 7. This illustrates an experiment in which the vibration generator moving at a frequency of 500/sec. was brought repeatedly into contact with the skin. Each time it touched the receptive field a short high frequency burst of impulses occurred, which soon terminated even though contact was maintained. At frequencies of 200/sec. to 250/sec. "hair" units were seen to follow for several seconds. Thus it would appear that some depression develops when the unit is driven continually at high frequencies.

A similar depression can be seen when the receptive field is stimulated electrically. If short current pulses (40  $\mu$ sec.) are delivered to the receptive field through a needle electrode inserted into the skin (the cathode of an electrode pair, the anode being remote), there is a single response to each electrical stimulus until a certain maximum frequency is reached. "Hair" units have been found to follow electrical stimuli at frequencies of 700/sec. to 1000/sec., but at these high frequencies the unit follows the stimulus in a one to one fashion for only a short time, after which every second or third electrical stimulus evokes a response. A further indication of developing depression can be found in the observation that the latency of the recorded responses is longer near the end of a high frequency train of impulses evoked by electrical stimulation than near the start of such a train. This increase in latency is typically 0.5 msec. to 1 msec. These observations suggest that high frequency activation of "hair" units, either electrically or mechanically, produces an incrementing depression. Catton (1961) has made similar observations while studying mechano-sensitive receptors in frog skin.

In an attempt to understand further the properties of "hair" units, it was considered of interest to determine the nature of the response to stimuli that differed only in texture. As described in the methods section, four plastic discs were used to give such stimuli. Onto the curved outer circumference



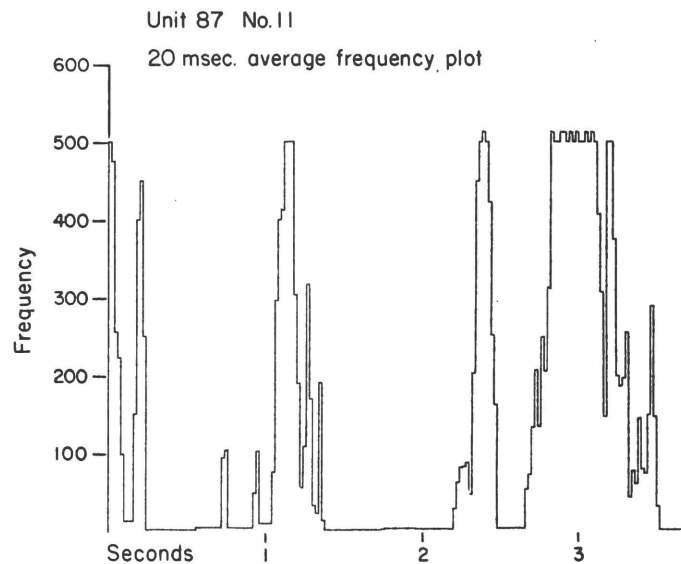


Fig. 7. The response of a "hair" unit to repeated application of a rod attached to the moving coil of a vibration generator. The coil was vibrating at a frequency of 500/sec. Each time the rod touches the receptive field the unit responds with a high frequency burst of impulses.

of three of the discs sandpaper, which differed in degree of coarseness, was glued. The fourth disc was left smooth. Human subjects handling the discs with closed eyes had no difficulty distinguishing between them. The discs were applied by hand, the curved outer circumference of the disc being moved across the skin of the receptive field. Fig. 8 illustrates the response of a "hair" unit to each of the four discs. Frequency is plotted as a function of time, the activity again being averaged over intervals of 20 msec. Every effort was made to keep the pressure of application and rate of movement of the discs the same in all cases. Fig. 8A shows that the response to the smooth disc was not especially large. Figures 8B, 8C, and 8D show that the responses to the discs with sandpaper were much larger, and that the responses were approximately equal regardless of the degree of coarseness of the sandpaper. Identical behavior was seen in all of the "hair" units investigated, and was not influenced by the presence or absence of hair on the receptive field. In the unit illustrated in Fig. 8 the receptive field had been depilated. As will be described later, the "tonic touch" units differed from the "hair" units in being sensitive to the degree of coarseness of the sandpaper used to activate them. In contrast, the type I units in the lateral columns responded equally well to all of the discs including the smooth one.

#### Responses to thermal stimuli

"Hair" units have also been examined for the presence of a response to thermal stimuli. Heating and cooling the receptive field by circulating water of different temperatures through a thermode applied to the field produced no response. Radiant heat was also without effect. When ethyl chloride was sprayed on the receptive field, activity occurred during the period of mechanical disturbance caused by the ethyl chloride application, but was almost always confined to this period. Occasionally two or three impulses occurred following the period of application. In fact, the most prominent effect of cooling the receptive fields of "hair" units was a reduction in the response to mechanical stimuli. Particular "hair" units differed greatly in the ease with which they were depressed by cooling, perhaps because not all lie at the same depth from the skin surface. The most easily depressed units were rendered completely inexcitable by spraying the receptive field with ethyl chloride, and almost all units showed some reduction in their response to mechanical stimulation. This could be shown most clearly by driving the "hair" unit with repetitive puffs of air applied to the clipped or depilated receptive field so that a stable response was obtained, and then, while the air stimuli continued unchanged, spraying the

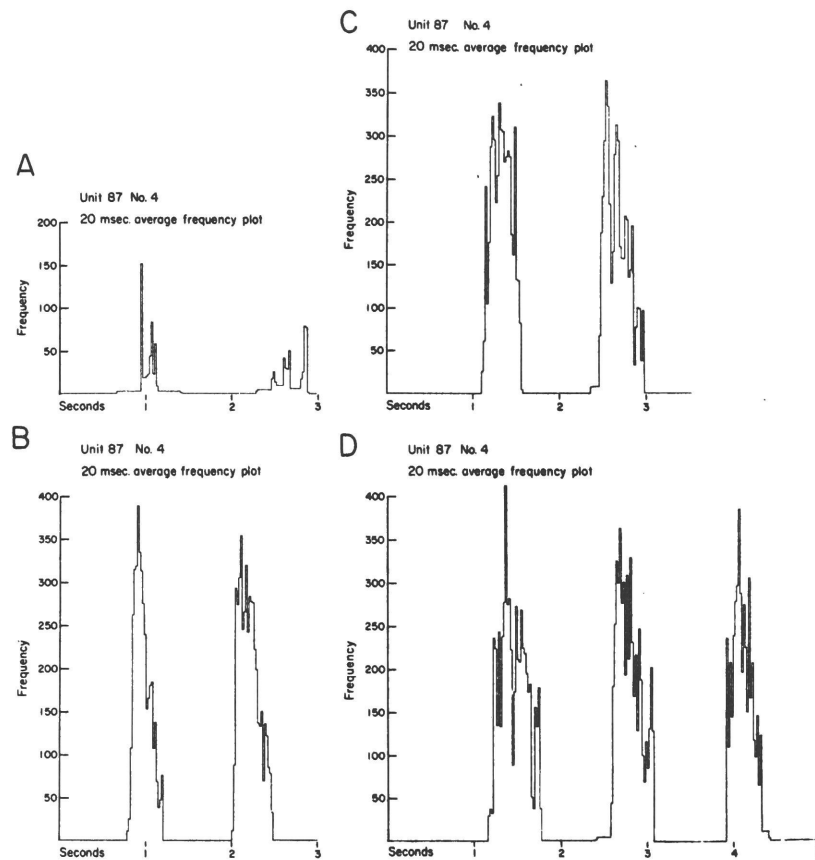


Fig. 8. Response of a "hair" unit to drawing stimulators of different texture across the depilated receptive field. Fig. 8A shows the response to the smooth disc, figures 8B, 8C and 8D to discs coated with sandpaper of increasing coarseness. It can be seen that the sandpaper covered discs activate the unit much more effectively than does the smooth disc, and that the response to each of the three grades of sandpaper is approximately equal.

receptive field with ethyl chloride. Cooling the receptive field in this way almost invariably led to a transient cessation of the response to the puffs of air. This reduction in the response to mechanical stimuli could be counteracted by warming the receptive field with radiant heat. The effect of ethyl chloride cooling was also tested on the responses of "hair" units to moving the finger across the receptive field. Sometimes the response of a particular unit to this stimulus was abolished altogether, but more often the cooling caused a reduction in the total number of impulses produced each time the stimulator was moved across the field, with a conspicuous absence of short intervals during the response. As will be discussed below, the mechanical responses of dorsal column units other than "hair" receptors were also depressed by cooling. But, in addition, the "tonic touch" units responded to cooling as such.

#### Responses to strong heating and strong mechanical stimulation

Attempts have been made to activate "hair" units by strong heating and with strong mechanical stimuli. By strong stimuli are meant those that cause pain in human subjects. In man, pain is felt when the skin temperature reaches  $45^{\circ}\text{C}$  to  $46^{\circ}\text{C}$  (Whyte 1951). In the present investigation, both radiant heat and the thermode have been employed. When the latter method was used the skin surface temperature could be determined. In no instance was heating through any temperature range found to initiate a discharge in "hair" units. If the temperature was increased to levels above about  $48^{\circ}\text{C}$ , the unit ceased to respond to mechanical stimulation. This was a persistent inactivation. At these temperatures the skin was markedly reddened and appeared to be damaged. The situation was somewhat similar when strong mechanical stimuli were applied. Such stimuli were usually obtained by using "noxious" clips or by crushing the skin with a device made especially for that purpose, but needles were also thrust into the receptive field, and hairs of the area pulled. None of these procedures was especially effective in activating "hair" units. The response of a "hair" unit to the "noxious" clip is shown in Fig. 5C. Strong mechanical stimulators seemed to cause a response which was proportional to the extent to which they caused movement of the skin and hair of the receptive field. Even when the receptive field was being crushed a discharge occurred only during actual movement of the crushing instrument, and this discharge was not of especially high frequency. Like strong heating, strong mechanical stimulation caused partial or complete elimination of the responses of "hair" units to the normally effective mechanical stimuli.

### Receptive fields of "hair" units

Before discussing the configuration of the "hair" unit receptive fields, it is necessary to examine the way in which receptive fields are determined, and to inquire into the significance of the term. Determined physiologically, the receptive field is that region of the skin from which impulses can be initiated by appropriate stimuli. A question of interest is the extent to which the physiologically defined receptive fields correspond to the location and extent of the morphologically defined receptor structures. It is possible that strong thermal or mechanical stimuli might spread to the receptor structure from areas more or less remote, and initiate a discharge. If this were so, then one would expect the size of the physiologically determined receptive field to be dependent on the strength of the stimulus used to measure it. This same result would also be obtained if the receptor terminals were somewhat spread out, but denser or more sensitive at their center. Using physiological evidence it would seem impossible to decide between these alternatives, and if it is found that the size of a receptive field is dependent on the strength of the stimulus, it would seem hazardous on the basis of physiological studies alone to make any statement about the configuration or extent of the morphological receptor structures. Also, in such circumstances, it is necessary to specify the strength of the stimulator used when indicating the size of a particular receptive field. As indicated below, "tonic touch" units typically show receptive field dimensions dependent on the strength of the testing stimulus. Such a dependence does not appear to be shown by "hair" units. Although the matter has not been studied in a properly quantitative fashion, "hair" unit receptive fields seem to show rather abrupt margins. Accurate mapping of "hair" unit fields requires that the overlying hair be either clipped or removed by depilation. If an area of skin which has been so treated is explored while recording from a single "hair" unit, there is what appears to be a sharp margin to the excitable area, sometimes without evident preliminary decline in the strength of the response as one approaches the edge of the field. "Hair" unit receptive fields generally do not show any clear gradation from a central region which is the most excitable to more peripheral regions which are progressively less excitable. In order to account for observations of this sort it is necessary to assume that the stimulus initiates activity only when delivered to the skin and hair overlying the receptor terminals, with little or no spread from regions outside the limits of the morphological receptor. Also, it is possible to inactivate completely a portion of a "hair" unit receptive field by strong heating or crushing, while the remainder of the field continues to respond.

These observations tend to support the notion that in the case of "hair" receptors, the receptive field determine physiologically corresponds in a general way to the morphological receptive field. All the "hair" unit receptive fields studied were located on the left hind limb of the experimental animal, as would be anticipated since recording was done exclusively from the left dorsal column at about the level of the fifth lumbar roots. In no instance did the field include glabrous skin. In some cases the field extended up to the margin of glabrous pad skin, but the receptive area always terminated abruptly at this point.

The size of "hair" unit receptive fields was found to be related to the location of the field on the hind limb. In general, the more distal the location of the receptive field the smaller its size, with those located on the digits being the smallest. These digital receptive fields were usually approximately circular in shape, and ranged in size from about 3 mm in diameter up to 10 mm by 5 mm for the largest field encountered, which was oval in contour. Most of the digital fields were less than 4 mm across. These figures are taken from a small population of digital units (total number = 5) in which mapping was done with some care. Somewhat larger fields were found on the dorsal and plantar surface of the foot between the ankle and the toes. These fields were usually oval in contour, with the long axis of the field oriented in the same direction as the long axis of the leg. Circular fields were also seen. In one case, where the field abutted the proximal margin of the glabrous skin of the large foot pad, the long axis of the field was parallel to the margin of the glabrous skin, and at right angles to the axis of the leg. Receptive fields on the foot varied in size from 5 mm in diameter for small circular fields up to 15 mm by 20 mm for the largest fields, which were oval. Fields of all intermediate sizes were found. The number of units with receptive fields on the foot which were mapped with reasonable care was again small, there being nine in all. Four "hair" units with receptive fields on the thigh and lower leg were adequately mapped. All the fields were oval, the smallest being 15 mm by 20 mm, the largest 25 mm by 17 mm. One field was considerably longer than it was wide, the dimensions being 10 mm by 35 mm. In addition to the units described above in which an attempt was made to map the receptive fields precisely, a number of "hair" units have been encountered in which a general impression of the field size has been obtained, though no actual measurements were made. These impressions have supported the notion presented above that "hair" units which are located distally tend to have smaller receptive fields. It is clear even from the small sample available here, that

at any particular proximodistal level receptive fields with a range of sizes can be found, with the smallest on the foot being smaller than the largest on the toes. Such variation is superimposed on an overall tendency for the distal fields to be smaller.

#### Summary of "hair" units

It is possible to summarize the behavior of "hair" units as follows. Spontaneous activity is absent. Mechanical stimuli which contact only the hairs of the receptive field are very effective in activating the units. They are best driven by high velocity but gentle mechanical stimuli such as air currents or the vibration generator. If the units are being activated by moving a stimulator of some sort across the skin of the receptive field, then, other things being equal, a coarse stimulator produces a higher frequency response than a smooth one. Crushing stimuli are no more effective than weaker stimuli, if both move the skin and hair to the same extent, and the strong stimuli tend to cause inactivation. Thermal stimuli are not effective in initiating a discharge from "hair" units. But both non-noxious cooling and noxious heating cause a reduction in the response of the units to mechanical stimuli. In the case of the cooling this inactivation is transient, but after strong heating, as after strong mechanical stimulation, the inactivation is not quickly reversible. Systematic studies of the duration of the inactivation resulting from strong stimuli have not been made. "Hair" units have ipsilateral receptive fields which tend to be smaller as the distal portion of the extremity is approached. The smallest receptive fields are only about 3 mm. in diameter. It can be seen that "hair" units are very specific with regard to the type of stimuli which are effective in activating them. They are poor candidates indeed for signalling information regarding temperature changes or tissue damage, since thermal stimuli do not activate "hair" units and tissue damaging stimuli inactivate them. They seem best suited for conveying information regarding discreet changes in the mechanical state of the body surface.

#### B. "Tonic Touch" Units

Properties of "tonic touch" units - gentle mechanical stimulation

Slowly adapting receptors in both hairy regions and glabrous pad skin have been included in a single category called "tonic touch" units. Receptors in these two different areas have many physiological properties in common, but also differ in certain respects. It is felt that some and perhaps all these differences may be attributable to the different types of epithelium with which the receptors

are associated. Still, it is possible that others would have preferred to classify separately the slowly adapting units in hairy and glabrous skin, and certainly such a classification would not be unreasonable. Whether the "tonic touch" receptors in glabrous and hairy regions are morphologically similar is not known, and in the absence of such information any classification of these receptors into the same or different categories must be tentative.

Fig. 9 shows the response of a "tonic touch" unit when the "firm" clip was placed on the receptive field. Figure 9A gives the overall course of the response, the frequency having been averaged over intervals of 0.5 sec. In this unit there was almost no activity in the absence of overt stimulation, and it has been a general finding that "tonic touch" units do not show an appreciable resting discharge. Some low frequency resting activity has been observed in about half the units studied, but in no case was this greater than 2 to 3 impulses per second. As the clip was applied there was a burst of activity which fell to a considerably lower frequency after the clip became steady. The response then underwent a further slow decline over a period of seconds and there was another burst of activity when the clip was removed. This is a typical response. Sometimes the activity continued to decline to complete cessation though the clip remained on the receptive field. However, when recording from any particular tonic unit, it was generally possible to apply a mechanical stimulator in such a way that the discharge continued for many minutes. Responses lasting 15 or 20 minutes have been observed and these were still in progress when the stimulator was removed. During prolonged activity of this sort the frequency was rather low, on the order of 5 to 10/sec. No particular study has been made of the longest durations of response obtainable. Fig. 9B is an average frequency plot of a portion of the response shown in Fig. 9A (the part between the arrows), but in Fig. 9B, the frequency has been averaged over intervals of 2 sec. This same portion of the response has been averaged over intervals of 20 msec. in the frequency plot labeled C. This plot shows a good deal more of the temporal structure of the response than the 2 sec. average plot in Fig. 9B. It can be seen that the discharge is rather irregular even though the stimulator is steady insofar as can be determined by visual inspection. Fig. 9D illustrates this irregularity in another way. Here the portion of the response shown in Fig. 9B has been plotted as an interval distribution histogram. It can be seen that a considerable range of intervals is present. It has been a quite consistent finding in the case of "tonic touch" units in both glabrous and hairy skin that the response to a steady



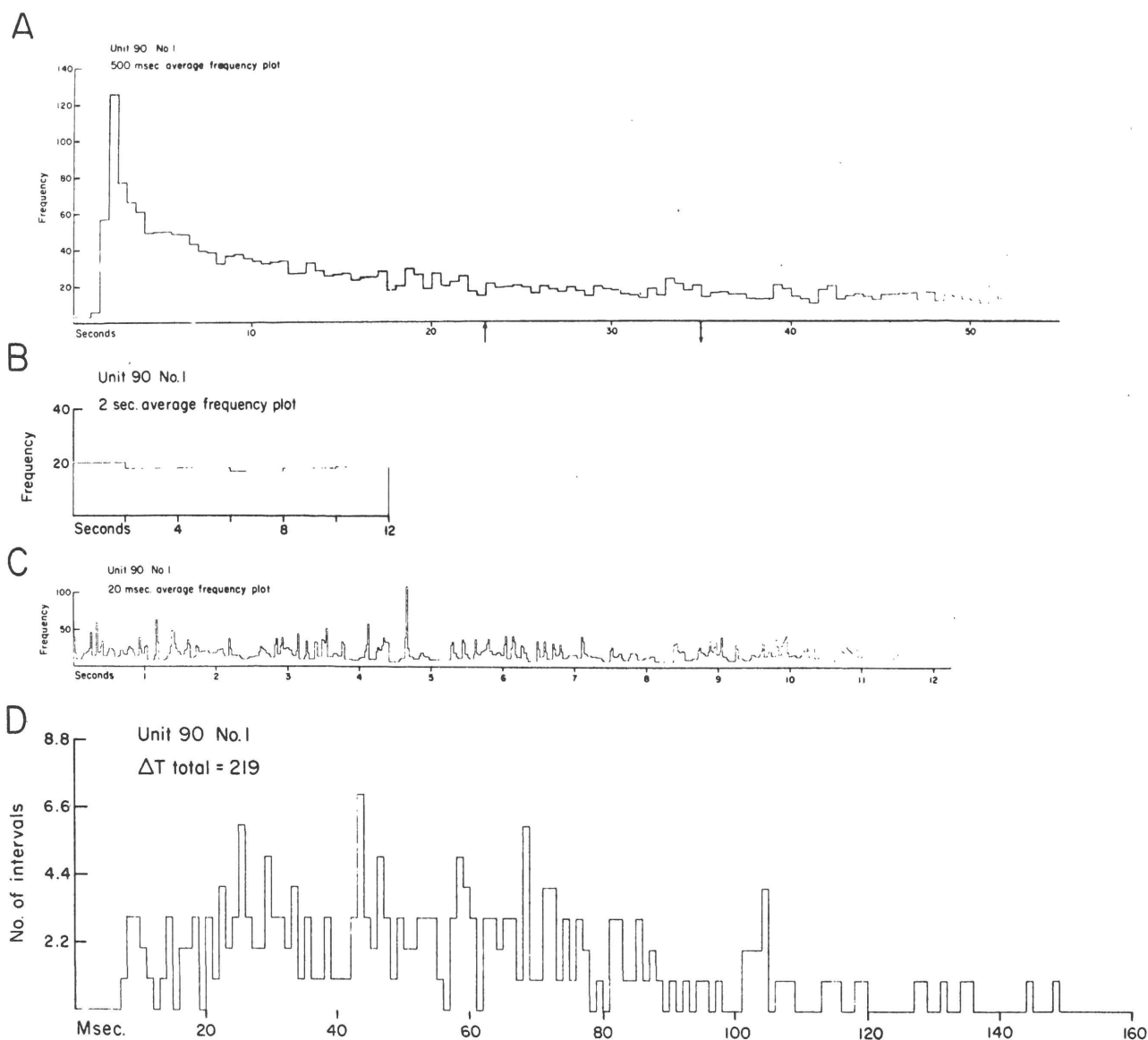


Fig. 9. Response of a "tonic touch" unit to a steady mechanical displacement of the skin caused by the "firm" clip. Fig. 9A shows the overall response, the frequency being averaged over intervals of 0.5 sec. The clip was applied at the beginning of the plot, and removed at the end. Fig. 9B shows that portions of the response which lies between the arrows in fig. 9A, the averaging interval now being 2 sec., and fig. 9C shows the same portion of the response with an averaging interval of 20 msec. Fig. 9D is an interval distribution histogram of the activity plotted in figures 9B and 9C. By examining figures 9C and 9D it can be seen that the response to maintained mechanical deformation of the skin is irregular.

mechanical displacement is irregular. A few units in glabrous skin have been exceptions, giving a low frequency and rather regular responses to a steady mechanical stimulator.

The principal differences seen between "tonic touch" units in glabrous pad skin and hairy skin relate to their responses to mechanical stimuli. It has been found that tonic units in hairy regions have lower mechanical thresholds than those in pad skin. The latter generally required stimulation with von Frey hairs measuring in excess of 200 mg if a response was to occur. The tonic units in hairy skin gave a quite conspicuous response in all cases tested when stimulated with a 20 mg von Frey hair, which was the weakest available. Perhaps the true mechanical threshold for these units is even lower. Indications of differences in threshold were also seen when the tonic receptors were activated with clip stimulators. The "mild" clip often initiated no maintained discharge whatever from tonic units in pad skin, but this stimulator was always effective in initiating such a discharge from units in hairy skin. The "firm" clip was a significantly better stimulator than the "mild" clip for the pad units, but the units in hairy skin responded equally well to both clips, suggesting that the "mild" clip was well above threshold for these units. It seems not unreasonable to suggest that the higher mechanical threshold of the tonic pad units is associated with the greatly thickened epithelium that covers the pads. This interpretation is perhaps supported by the fact that two tonic pad units with receptive fields just at the margin of the pad, where the epithelium is less thick, had considerably lower thresholds than the average figures given above. One of these units in fact responded to a 20 mg von Frey hair. However, much more must be known concerning the mechanical properties of the relevant skin areas before such suggestions can be considered seriously. Another difference between tonic units in hairy and pad skin not so readily explained is that tonic pad units generally fired at lower frequencies, especially when the stimulator was maintained steady, than did the tonic units in hairy skin. This was true regardless of the strength of the stimulator.

The responses of tonic units to the vibration generator have not been sufficiently studied to allow any statement concerning their behavior when excited in this way. Air currents have been employed when studying tonic pad units, and in all the cases examined no response has occurred to either a continuous or interrupted stream of air. This is a further indication of the rather high mechanical thresholds of these units. The tonic units in hairy skin have been

observed to respond to hair movement, the stimulator being in this case the hair brush, but activation by air currents has not been studied. The response of the tonic units in hairy skin to hair movement is much less vigorous than the response to stimulating the skin and hair together.

All the tonic units examined have shown velocity sensitivity. Fig. 10 shows the response of a tonic pad unit to moving the finger across the receptive field at different rates. Fig. 10A is a 20 msec. average frequency plot of the response to moving the finger across the field rather slowly; Fig. 10B shows the response when the finger was moved more rapidly. Figures 10C and 10D are interval distribution histograms of the responses shown in Figures 10A and 10B respectively.

Another effective stimulator for tonic units, studied satisfactorily only with pad units, is an object with a pointed tip. The response to such a stimulator is best shown by stimulating the receptor with lucite discs of progressively smaller diameter. By mounting these on the plunger of a syringe filled with air at constant pressure it has been possible to keep the force constant while the stimulating tip diameter was varied. Using this method it was found that the highest frequency responses were obtained with the stimulators having the smallest tips. Again, velocity sensitivity could be demonstrated, a particularly effective way to stimulate tonic pad units being rapid displacement of the skin with a stimulator having a small tip diameter.

As in the case of "hair" units, "tonic touch" receptors have been found to respond better to coarse stimulators than to smooth ones, other factors being equal. The situation differs from that observed in hair units however, where the response was found to be equally large regardless of the coarseness of the sandpaper moved across the receptive field. Fig. 11 shows the response of a tonic pad unit to stimulators differing only in texture. Each plot shows the frequency as a function of time, the frequency being averaged over a period of 20 msec. Fig. 11A shows the response to the smooth stimulator, Fig. 11B the least coarse, Fig. 11C the intermediate, and Fig. 11D the coarsest sandpaper. It is evident that the discharges in Figures 11A and 11B were about equal and smaller than the discharges in Figures 11C and 11D. The last two were again about equal, though the discharge shown in Figure 11D might have been slightly larger. Other tonic pad units have shown somewhat different behavior, giving a response of different magnitude to each of the discs, except the intermediate and coarsest sandpaper, where the responses were the same. No units have been

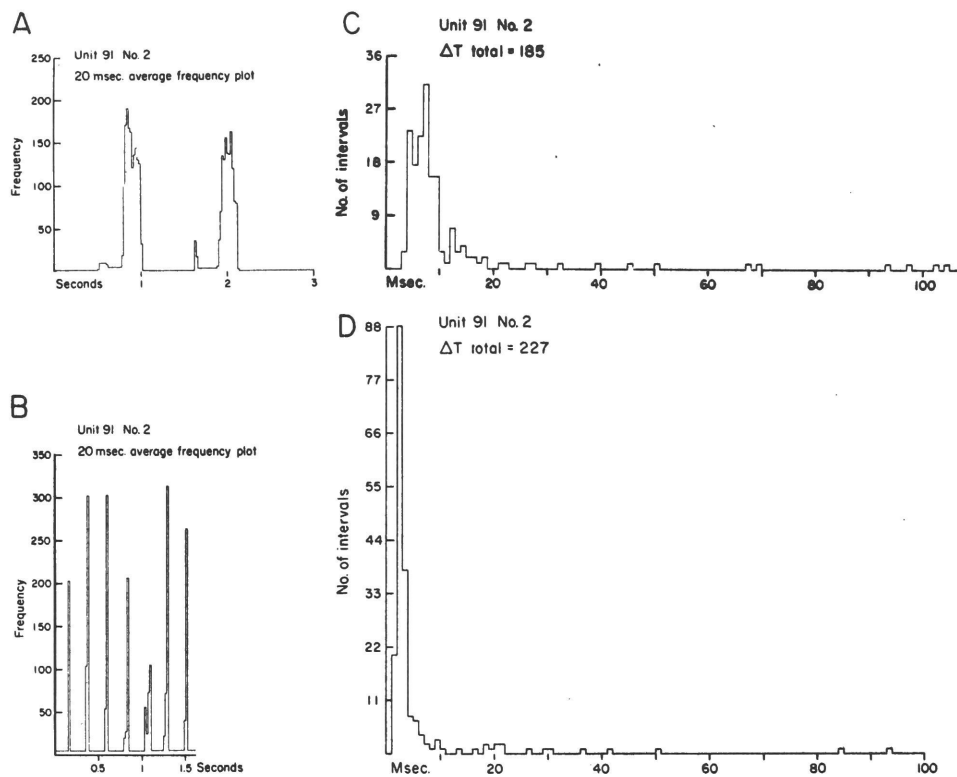


Fig. 10. Response of a tonic pad unit to moving the finger across the receptive field at different velocities. Fig. 10A shows the response to moving the finger twice, rather slowly, across the receptive field; and fig. 10C is an interval distribution histogram of this activity. Fig. 10B illustrates the response to repeatedly moving the finger rapidly across the field, and fig. 10D is an interval distribution histogram of this response. A comparison of these responses indicates that the unit displays velocity sensitivity.

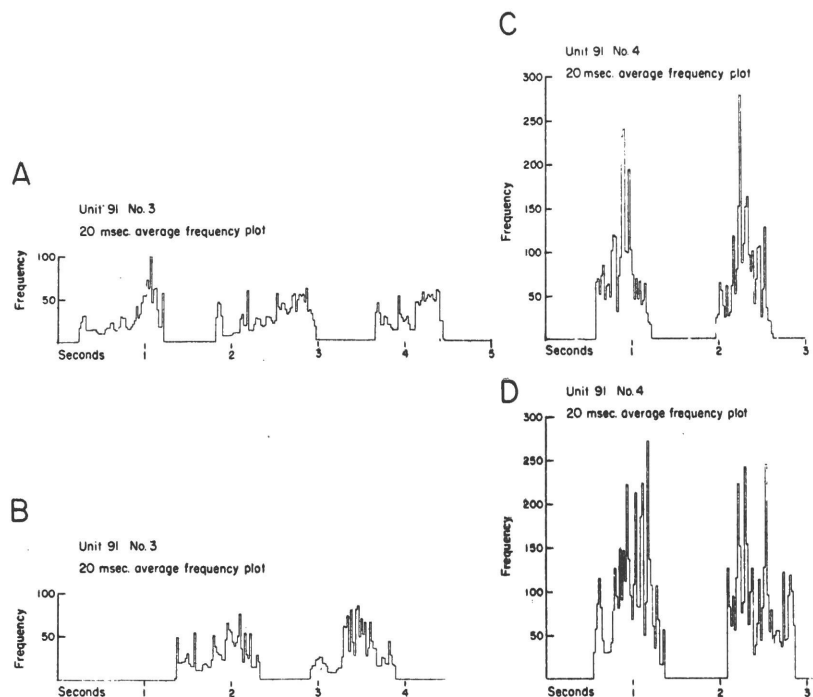


Fig. 11. Response of a tonic pad unit to stimulators differing in texture. In fig. 11A the smooth disc is drawn across the receptive field three times. In figures 11B, 11C and 11D the least coarse, intermediate, and coarsest disc respectively are each drawn twice across the receptive field. The responses in 11A and 11B are approximately equal, as are those in 11C and 11D.

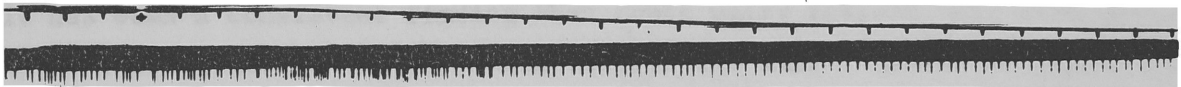
seen which distinguish well, on the basis of simple firing frequency, between the intermediate and coarsest sandpaper. Unlike tonic pad units, tonic units in hairy skin have not been examined satisfactorily with stimulators of different texture. In the few attempts that have been made to stimulate these units, the coarser materials have resulted in a depression of mechanically evoked activity. However, one of the receptors mentioned previously having a receptive field at the margin of the pad skin and a low threshold to mechanical stimulation has been investigated. In this unit the response increased as the stimulators became coarser, except that the intermediate and coarsest sandpaper gave about equal activation. Curiously, the smooth disc caused a much less vigorous response in this unit than it did in other less sensitive pad units. Thus it would appear that the nature of the response to stimulators of different texture is not related in a simple way to the threshold of the receptor. It is unknown just what aspects of the stimulator and what properties of the receptor determine the nature of the response to different textures.

#### Responses to thermal stimuli

##### A. Responses to cooling

A particularly interesting aspect of the behavior of "tonic touch" receptors concerns their response to thermal stimuli. The response to cooling has been studied most thoroughly, and in almost all tonic units examined a discharge occurred when the unit was cooled sufficiently rapidly. In a number of instances ethyl chloride has been used to study these responses, but the best controlled and most satisfactory studies can be made using the thermode. In one tonic pad unit circumstances were especially favorable and a somewhat more complete analysis than usual was possible. In this instance the pressure of the thermode on the receptive field caused a maintained mechanically induced discharge which, as is typical of these units, was irregular. Slow cooling of the receptive field from near  $33^{\circ}$  to about  $27^{\circ}\text{C}$  simply caused a cessation in the mechanically induced activity. More rapid cooling through the same temperature range caused the frequency of the discharge to increase somewhat, though it remained irregular. Likewise, cooling the receptor from  $40^{\circ}$  caused an irregular discharge. If the temperature was first lowered slowly to  $27^{\circ}$ , which silenced the mechanically evoked activity, and the temperature was then lowered more rapidly to  $18^{\circ}$  or so, a regular discharge ensued. Cooling slowly from  $27^{\circ}$  to  $18^{\circ}$  produced no discharge. Some features of this response are illustrated in Figure 12. One beam of the oscilloscope displayed the skin surface temperature

A



B

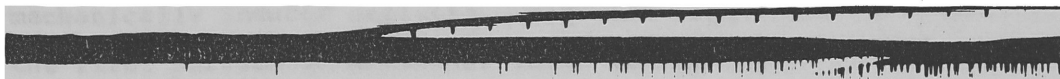


Fig. 12. Activity in a tonic pad unit in response to pressure and cooling. The upper trace in fig. 12A displays the temperature and time marks at intervals of 1 sec.; the lower trace shows action potentials. The initial temperature in fig. 12A is near  $35^{\circ}\text{C}$  and the irregular activity which can be seen at this time is due to pressure of the thermode on the receptive field. At the mark on the upper trace ice water is turned into the thermode and the temperature falls to a final value of  $22^{\circ}\text{C}$ . There is an increase in the irregular activity as the temperature begins to fall, but the later part of the response to cooling is clearly regular. In fig. 12B the initial temperature is  $19^{\circ}\text{C}$ . Warm water is turned into the thermode near the beginning of the record and causes an increase in the skin surface temperature to a final value of  $32^{\circ}\text{C}$ . There is a resumption of mechanically evoked activity as the receptive field is warmed, and this activity is irregular.

and time marks occurring every sec., the other beam displayed action potentials. Initially the temperature of the skin was near  $35^{\circ}$  in Fig. 12A. The square deflection on the temperature trace indicates the time at which ice water was turned into the thermode. Some increase in activity occurred just as the temperature began to fall, but the regular activity did not begin until somewhat later, when the temperature was falling through a lower range. At the end of Fig. 12A the temperature had fallen to  $22^{\circ}$ . Fig. 12B shows the resumption of mechanically induced activity as the receptive field was warmed. Here the initial temperature was  $19^{\circ}$ , and though the temperature was low, activity was virtually absent. It has been a consistent finding that tonic units respond only when the temperature is falling and not after it has reached its final value. The fact that the unit illustrated here and other tonic units did not respond to slow cooling further illustrates this point. The final temperature reached in Fig. 12B was near  $32^{\circ}$ , and it can be seen that warming resulted in the resumption of irregular mechanically induced activity. Fig. 13A illustrates graphically the response, the first portion of which was shown in Fig. 12A. This is an average frequency plot in which the averaging interval is 2 sec. The vertical line shows the time at which the ice water was turned into the thermode. Fig. 12B shows the response, the first portion of which was shown in Fig. 12B. This again is a frequency plot employing a 2 sec. averaging interval. Figures 13C and 13D are designed to show the degree of regularity in the responses graphed in Figures 13A and 13B. Figures 13C and 13D are interval difference plots of the data shown in Figures 13A and 13B respectively. The way in which interval difference plots are made has been described in Methods. In each case only the portion of the response between the arrows is analysed. Though the average frequencies of the responses to thermode pressure and cooling were similar, the response to cooling shown in Fig. 13C was more regular than the response to thermode pressure. This too has been a consistent finding. Whenever a tonic unit has been seen to respond to cooling, this has been, at least in its final part, a regular response. In almost all instances this response to cooling has been considerably more regular than mechanically evoked activity of a corresponding frequency. Another consistent finding, however, is that cooling through a range of temperatures somewhat higher than the range which causes regular discharge can elicit activity which is irregular. Therefore, it would appear that the nature of the response of "tonic touch" units to cooling depends on the temperature through which the cooling occurs, and that the response to cooling can not always be distinguished on the basis of pattern from the response to mechanical stimulation. It is possible to



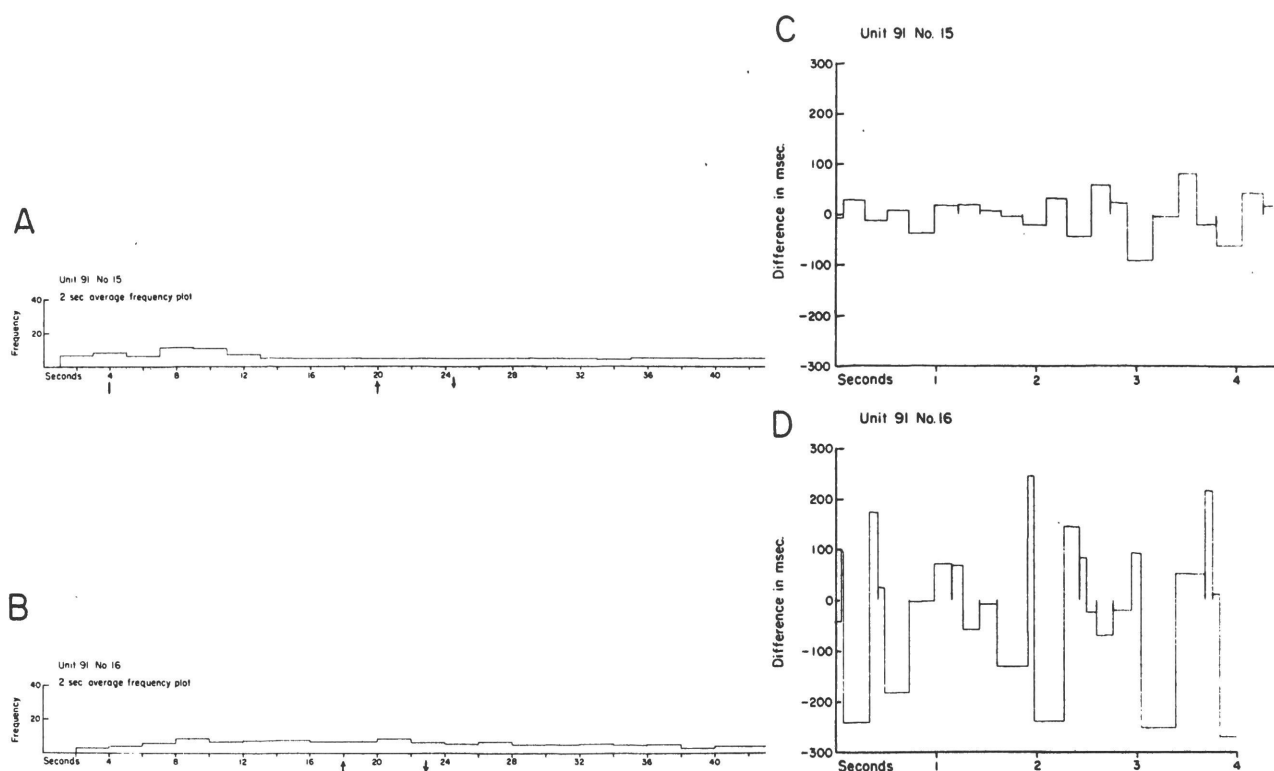


Fig. 13. The same response shown in fig. 12. Fig. 13A shows the response of the unit to cooling. Ice water was turned into the thermode at the vertical mark. The initial activity in the unit is due to thermode pressure. Fig. 13C shows an interval difference plot of that portion of the response which lies between the arrows in fig. 13A. Fig. 13B shows the reappearance of mechanically evoked activity in this unit as the receptive field is warmed, and fig. 13D is an interval difference plot of that portion of the response which lies between the arrows. It can be seen by comparing figures 13C and 13D that the mechanically evoked activity is considerably less regular than that elicited by cooling.

imagine, however, that the portion of the response to cooling which is regular might have different informational significance for the animal than the irregular activity which results in response to mechanical stimulation and cooling through higher temperatures.

One aspect of the behavior of tonic units to cooling should be noted. These units appear to show a response to cooling as such, because cooling will cause a discharge at temperatures where the response to mechanical stimulation is clearly depressed. If this were not so it might be possible to consider the increased activity evoked by cooling as a reflection of an enhanced response to mechanical stimulation, it being argued that cooling had moved the temperature to a level which was more nearly optimal for the mechanical response.

#### B. Response to heating

Tonic units have also been seen to increase their activity in response to heating. This particular response has been studied only while recording from tonic pad units, and it is not known whether tonic units in hairy regions show this kind of thermal sensitivity. In contrast to the response to cooling, where the temperature had to be falling for activation to occur, the response of tonic pad units to increased temperatures occurred only after the temperature became reasonably steady. In fact, somewhat rapid increases in temperature in the range of 35°C to 40°C seemed to cause an inhibition of activity. This inhibition has been seen as a cessation, while the temperature was rising, of the mechanically induced activity which resulted from thermode pressure. Inhibition was suggested also by the finding that the discharge which occurred as a result of warming did not appear while the temperature was rising, but began only after reasonably steady temperature levels were reached. If the thermode is used, there is always some question as to whether the activity which appears at elevated temperatures might not be due to a heightened sensitivity of the receptor to thermode pressure. As yet, no careful studies have been made of the mechanical excitability of tonic pad units as a function of temperature, although it was noted, as mentioned above, that tonic units were depressed when the skin surface temperature fell much below 30°C. Warming the skin by the radiant method allows one to appraise the response of these units in the absence of overt mechanical stimulation, and raising the temperature by this means was generally effective in initiating a discharge. It is nevertheless possible that even in the absence of intentional activation, the receptor was still subject to some form of suitable mechanical stimulation, perhaps by virtue of its position

in the skin, even in those cases where there was no resting discharge. Thus it is not possible to state whether or not tonic pad receptors respond to heating as such, or whether the response at elevated temperatures was due to some increased sensitivity to mechanical stimulation. The exact skin surface temperatures at which tonic pad units begin to discharge have not yet been properly studied. In general, the effective temperatures have been rather high ( $40^{\circ}\text{C}$  or above) but not so high as to cause damage to the receptor, this being indicated by the absence of any depression in the response of the unit to mechanical stimulation. The activity resulting from heating has always been of low frequency (less than 5/sec.), and it has invariably been irregular.

#### Responses to "noxious" stimulation

"Tonic touch" receptors in both glabrous pad skin and hairy skin have been studied to determine the nature of their reaction to strong mechanical stimulation - stimuli which cause pain in human subjects. The tonic receptors in hairy skin were found to be especially readily inactivated by various kinds of mechanical stimulation, and in a number of cases the inactivating stimuli were not particularly noxious. Mention has already been made of the fact that moving coarse sandpaper over the receptive field of one such unit resulted in partial inactivation. In another instance, pressing several times on the receptive field with a Von Frey hair caused some depression. The first obvious manifestation of inactivation in these units, and in all the slowly adapting mechanoreceptors seen, was failure of the tonic component of the response, though at the same time there was often some reduction in the response to moving stimuli. As inactivation became more pronounced, the response of the receptors to movement decreased, until, in the case of complete inactivation, no response whatever could be obtained. Tonic pad units were somewhat more resistant to the inactivating effects of strong mechanical stimulation than were the tonic receptors in hairy regions. Often, however, they showed reduced responsiveness after application of the "noxious" clip, and in one instance which was well studied, repeated application of the "firm" clip caused partial inactivation. Tonic pad units always discharged at a considerably higher frequency when stimulated with the "firm" clip than when the "mild" clip was used. The "noxious" clip generally caused a tonic response which was less vigorous than that which was initiated by the "firm" clip, probably because of the inactivating effects of the "noxious" clip. It was usually possible by proper application of the "noxious" clip or some other crushing stimulus to initiate a transient high

frequency discharge in tonic pad units. This was followed by an inactivation which was often complete. Fig. 14 shows such a response. Here the receptive field of the tonic pad unit was crushed with a haemostat. It can be seen that the discharge terminated abruptly although the stimulator remained on the field. Further efforts to excite this receptor were without effect.

It should be noted that tonic pad units differ from "hair" units in the nature of their response to strong mechanical stimulation. "Hair" units, though inactivated by strong crushing stimuli, showed no transient high frequency discharge of the sort displayed by tonic units in response to inactivating stimuli. A few tonic pad units behaved like "hair" units in this respect, and tonic units in hairy regions were partially inactivated without any associated high frequency discharge. It may be that the placement of the stimulator providing the strong mechanical stimulation determines whether a high frequency discharge will occur.

Strong mechanical stimulation other than crushing has also been employed in the study of tonic pad units. It has already been noted that these units responded with progressively higher frequencies as the diameter of the mechanical stimulator became smaller, the force being held constant in all cases. Very small diameter stimulators cause pain when applied to human subjects. If two stimulators are chosen, both with small diameters, one of which is painful to humans and the other not, and the responses of tonic pad units to these two stimulators compared, it is found that the discharges are of about equal magnitude. This experiment has been done with the stimulators attached to the plunger of an air filled syringe (see methods) so that the force exerted by each was the same. If a needle is pressed against the receptive field a comparable discharge is obtained. Thus it would appear that these units are unable to distinguish between pointed mechanical stimulators which are painful and non-painful in man.

The effect of strong heating on tonic pad units has also been examined. It was found that these units were partially or wholly inactivated by raising the skin surface temperature higher than 47°C or 48°C. Inactivation was not associated in this case with any high frequency discharge, and in general tonic pad units resembled "hair" units in the nature of their reaction to high temperatures. The effect of high temperatures on tonic units in hairy skin has not been studied.

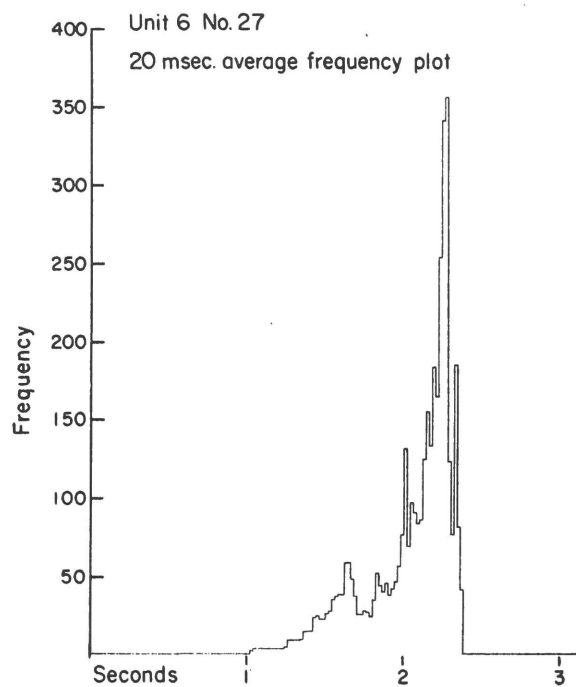


Fig. 14. Response of a tonic pad unit to crushing the receptive field with a haemostat. The response terminated abruptly even though the haemostat remained on the skin. The unit was inactivated by this stimulus.

### Receptive fields

Reference has already been made to the fact that the dimensions of "tonic touch" unit receptive fields vary with the strength of the stimuli used to determine them, it being generally possible to evoke activity from a larger area with stronger stimulation. Using the weakest effective stimulus a discharge can be evoked from one, or in some cases, two points which are of small size (1 mm to 2 mm across). With stronger stimuli the receptive region can be enlarged somewhat, an area 3 mm to 4 mm in diameter now being excitable. Careful studies of receptive field dimensions have been made on tonic pad units only, but it can be said that tonic units in hairy skin have receptive fields which are also of small size (2 mm or 3 mm in diameter). Another type of behavior displayed by tonic pad units concerns the duration of the discharge which is elicited by a stimulator as it is moved from one part of the receptive field to another. It has been observed that tonic pad units respond with a less well maintained discharge if the stimulator is placed on the peripheral parts of the field, while the rate of adaptation seems to be slowest if the central most excitable portion of the receptive field is stimulated. Tonic units in hairy skin have not been investigated in this respect. In all but a few cases, the small receptive fields of tonic units have been approximately circular in shape. The exceptions have been tonic pad units with receptive fields at the margin of the pad skin. These units possess elongated receptive fields, the long axis being parallel to the pad skin margin. As mentioned above, these units showed low thresholds to mechanical stimulation, presumably because the skin is less thickened at the margins of the pad. For reasons already indicated when discussing "hair" unit receptive fields, no statements can be made concerning the exact dimensions of the touch unit receptor structure, though it is obvious that the receptor must be small. Also it is to be noted that touch unit receptive fields are of approximately the same size wherever they occur on the surface of the hind limb, and do not, like "hair" units, tend to be smaller the more distal their location.

### Summary of tonic units

In summary, it is possible to say that tonic units respond to maintained mechanical displacement with a maintained irregular discharge which falls gradually over a period of seconds or minutes to rather low levels (5 to 10 per sec.) which may be maintained for many minutes. The tonic discharge is at all times considerably lower in frequency than that which can be obtained by rapidly moving some rough material over the receptive field, or rapidly pressing it with a small

diameter stimulator. In other words, tonic units show velocity sensitivity. Strong mechanical stimulation and strong heating result in partial or complete inactivation of these units. If the strong mechanical stimulation is in the form of crushing the receptive area, tonic units have been seen to give off a transient high frequency discharge prior to inactivation. This discharge is comparable in frequency with that which occurs when coarse sandpaper is rapidly drawn across the receptive field. Tonic units respond to maintained non-noxious elevated temperatures with a sustained irregular discharge of low frequency. There is evidence that while the temperature is increasing the excitability of the units is depressed. They respond during cooling with a transient low frequency discharge which may be regular or irregular depending on the temperature range through which the cooling occurs. The frequencies of the discharges occurring in response to thermal stimuli are of roughly the same magnitude as the discharge which occurs late in the tonic phase of the response to maintained mechanical stimulation. These frequencies are less than 10% of the maximum frequencies (averaged over 20 msec.) that can be obtained from these receptors by appropriate high velocity mechanical stimulation. Tonic units possess small spot-like receptive fields which are approximately the same size regardless of where they are found on the hind limb. The receptors seem best suited to convey information about rapid mechanical events occurring at the surface of the body. They seem unsuited to convey information concerning tissue damage because they are inactivated by strong mechanical stimulation and strong heating. It is difficult to understand how they alone could convey information concerning an increase in skin temperature, since the irregular pattern of activity in response to warming and mechanical stimulation is similar. The regular activity which can occur in response to cooling does seem sufficiently different from the mechanically induced discharge to perhaps convey the information that the skin temperature is falling, assuming that the central nervous system is able to distinguish between regular and irregular patterns of activity. No information seems to be available concerning the capacities of the central nervous system in this respect.

#### C. "Phasic pad" units

##### General properties

Another type of unit found in the dorsal columns has been called the "phasic pad" unit. Five units of this type have been seen, two of which have been well studied. As the name indicates, these units have receptive fields limited to pad skin, and thus far such receptors have been found only in the principal pad.

They are very rapidly adapting, and respond like "hair" units to clip stimuli, there being a discharge only when the skin is moved. They are especially well driven by the vibration generator, and will quite readily follow frequencies of 500/sec., the highest that has been studied. Like "hair" units, "phasic pad" units will follow the stimulator at 500/sec. for only a certain period, though in the case of pad units the duration of the period during which following can be obtained is longer (0.5 sec. or more) than with "hair" units. Intermittent currents of air were ineffective in initiating a significant discharge from "phasic pad" units, and from tonic pad units as well, in contrast to the vigorous response shown by "hair" units to this stimulus. Like "hair" units and tonic units, "phasic pad" units responded with a higher frequency discharge when rough surfaced material was moved across the receptive field than when a smooth stimulator was used. Fig. 15 shows the response of a "phasic pad" unit when the disc stimulators used previously were drawn across the receptive field. Fig. 15A shows the response to the smooth disc; Figures 15B, 15C and 15D to discs coated with sandpaper of increasing coarseness. It can be seen that the response to the least coarse sandpaper was considerably greater than the response to the smooth disc, and that the response to the intermediate grade of sandpaper was somewhat larger than the response to the least coarse. The responses to the intermediate and coarsest sandpaper appear about equal, though the response to the coarsest sandpaper may have been slightly larger. Thus it would seem, limiting consideration to the magnitude of the responses only, that this unit might allow some discrimination of at least three of the four textures used to activate it. The largest increase in frequency occurs in the transition from the smooth disc to the least coarse sandpaper.

Like the other receptors described thus far, "phasic pad" units show velocity sensitivity. This is illustrated in Figure 15C and Figure 16. In 15C the intermediate grade of sandpaper was moved slowly across the receptive field; in 16A this same stimulator was moved quickly across the field. The frequencies attained were considerably higher when the stimulator was moved rapidly. Note that there was no activity in the absence of stimulation in any of the responses illustrated. Phasic pad units have typically shown no spontaneous activity. Figure 16B and 16C show interval distribution histograms of the responses plotted in Figures 15C and 16A respectively.

The responses of phasic pad units to thermal stimuli have not been studied in detail, but thus far the attempts to so activate them have been unsuccessful.



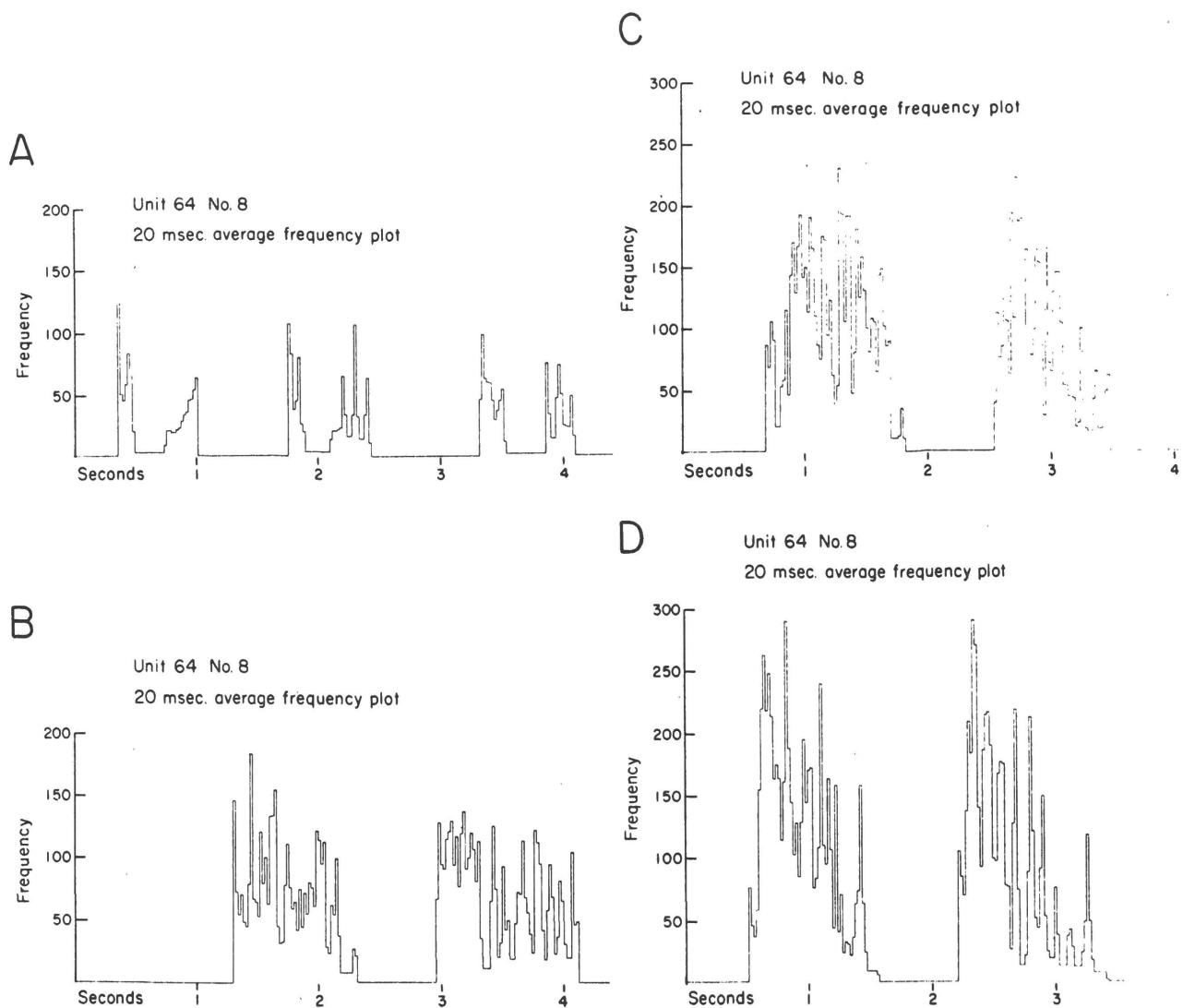


Fig. 15. Response of a "phasic pad" unit to stimulators of different texture drawn across the receptive field. Fig. 15A shows the response to the smooth disc, figures 15B, 15C and 15D to discs coated with sandpaper of increasing coarseness. It can be seen that the responses are of progressively higher frequency as stimulators of increasing coarseness are applied.

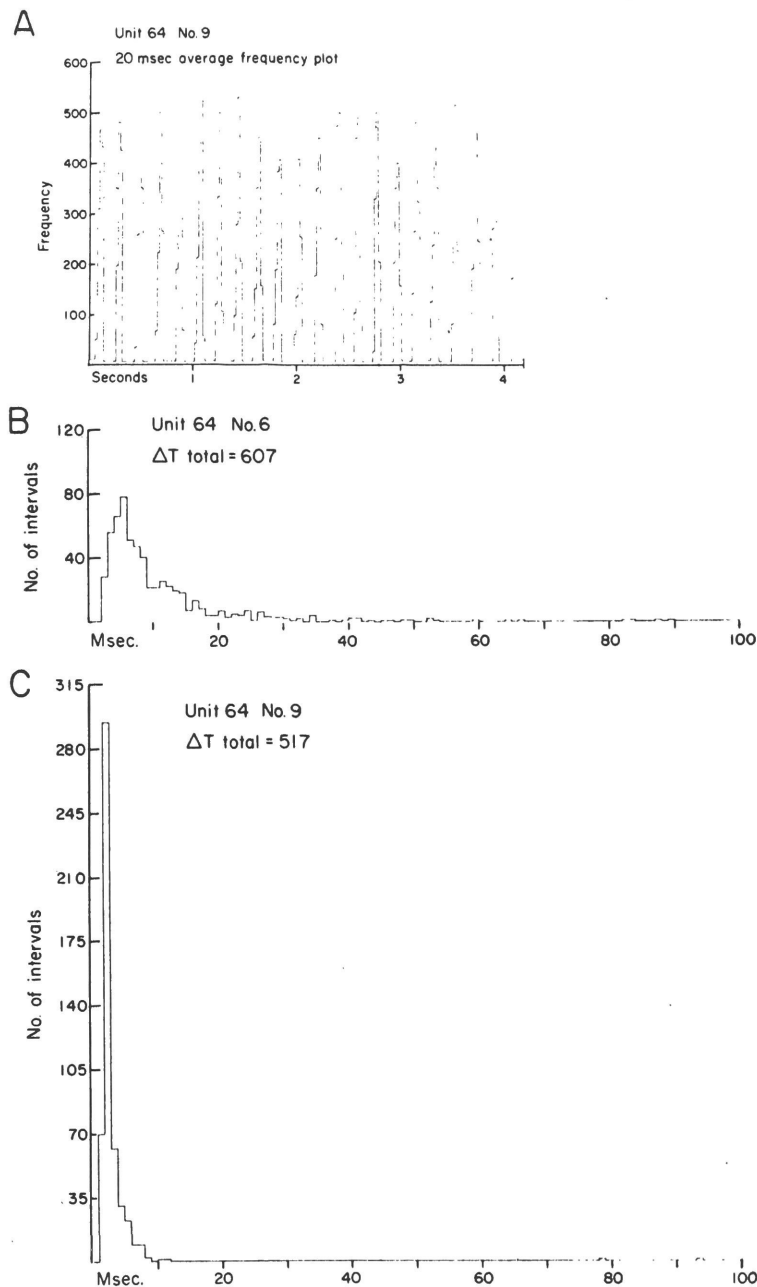


Fig. 16. Fig. 16A shows the response of a "phasic pad" unit to rapidly moving the intermediate grade of sandpaper across the receptive field. This discharge is to be compared with that illustrated in fig. 15C which shows the response of this same unit when the intermediate grade of sandpaper is moved slowly across the receptive field. Figures 16B and 16C are interval distribution histograms of the responses shown in fig. 15C and fig. 16A respectively. A comparison of the responses to slow and rapid stimulation indicates that "phasic pad" units show velocity sensitivity.

Cooling with ethyl chloride has been seen to depress the responsiveness of these units to mechanical stimulation, and strong heating to cause complete inactivation. The effects of strong mechanical stimulation have not been well studied, though it has been noted that the application of the "noxious" clip produced a discharge from phasic pad units which was proportional to the extent and speed with which the clip moved the skin, and hence the resultant activity might be no greater than the response to the "firm" or "mild" clip. Whether strong mechanical stimuli produce inactivation has not been determined.

#### Receptive fields

Like tonic pad units, the size of "phasic pad" unit receptive fields depends on the strength of the stimulator used, the stronger stimulators activating the units from larger areas. The dimensions of "phasic pad" unit receptive fields are somewhat larger than the receptive fields of tonic pad units, being 3 mm to 6 mm in diameter as compared with the 2 mm to 4 mm receptive fields found for tonic units. Whereas most of the tonic unit receptive fields seemed quite "spot-like", the fields of "phasic pad" units could be better described as regions of sensitivity. Armett and Huntsperger (1961) have mapped the receptive fields of "phasic pad" units in a more quantitative fashion than has been done in this investigation, and the present results are in agreement with their data.

#### Summary of "phasic pad" units

To summarize, "phasic pad" units have been best driven by stimuli which produce a high velocity displacement of the skin, such as the vibration generator, or rapidly moving some rough material across the receptive field. They are rapidly adapting and show velocity sensitivity. There is no resting activity. Their responses to thermal stimuli have not been well studied, but thus far no activation by such stimuli has been observed. Inactivation occurs when the skin surface temperature is increased above 46°C or 47°C, and ethyl chloride cooling causes a transient decrease in excitability. Strong mechanical stimulation causes no better response than a weak stimulus if the two move the skin equally. "Phasic pad" units typically have lower mechanical thresholds than tonic pad units, though they are not as sensitive to mechanical stimuli as the tonic units in hairy skin.

#### D. Units with subcutaneous receptors

Units which are activated by stimulating structures deep to the skin are not of immediate concern to the problem of how different modalities of cutaneous sensation are appreciated. Such deep units do nevertheless possess some interesting properties which contrast in certain respects with those of cutaneous

receptors. Fig. 17 shows resting activity recorded from a unit which could be activated by extending the toes. Fig. 17A shows the frequency of this activity averaged over two second intervals. Fig. 17B shows an interval distribution histogram of the data plotted in Fig. 17A, and Fig. 17C shows an interval difference plot of this same data. As can be seen the discharge was regular. It is interesting to compare this pattern of discharge with activity recorded from slowly adapting cutaneous units, where a much less regular discharge was seen at comparable frequencies. All the slowly adapting units studied in these experiments which could be activated by stimulating deep tissues have shown a regular discharge in response to maintained stimulation. In addition, resting activity is common in deep units, and all such units have shown velocity sensitivity.

Thus striking differences can be seen between the patterns of discharge evoked by maintained mechanical stimulation in units which terminate in the skin and units which terminate in subcutaneous structures. In this case, however, the different patterns of activity are associated with the location of the receptor and not with the kind of stimulation used to activate it. Lippold et. al. (1960) have shown that muscle spindles respond not only to stretch but also to cooling, and that the discharge is regular in both cases. If patterns of activity have any functional meaning in the cat nervous system, the obvious differences in pattern between dorsal column units with cutaneous and deep receptors deserve further consideration.

One more comparison between deep and cutaneous units may be of interest. A deep receptor which is particularly favorably located for study responds to stimuli which cause claw movement. A number of units of this type have been seen, and they appear to form a quite homogenous group. Each unit is associated with only one claw, and can be activated either by protruding the claw or by pressure to tissues around the base of the claw. This latter fact makes it possible to stimulate these units with the clips used to activate skin afferents. Fig. 18A shows the response of one of these units when the "firm" clip was applied to the base of the claw. The frequency here is averaged over 20 msec. intervals. As can be seen, the discharge showed typical regularity. Fig. 18B shows a similar plot of the response of this same unit to the "noxious" clip. In this case, the initial frequency was quite high, but the activity was not maintained, and even though the clip remained on the sensitive area, the unit stopped discharging. It is also evident that the mechanism responsible for the

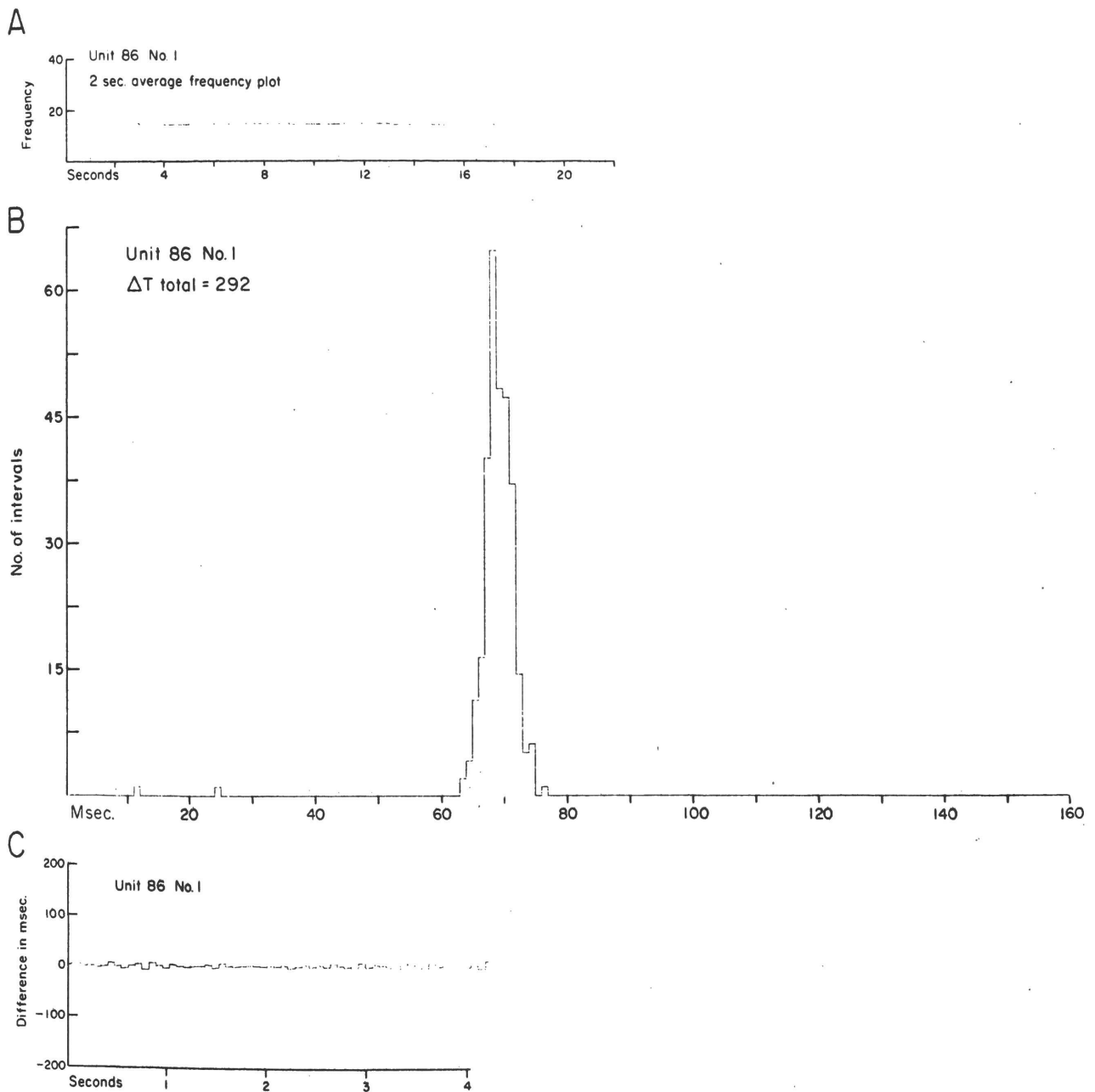


Fig. 17. Resting activity in a subcutaneous unit which could be activated by extending the toes. Fig. 17A shows the activity averaged over 2 sec. intervals. Fig. 17B is an interval distribution histogram of this same activity, and fig. 17C is an interval difference plot. The activity can be seen to be quite regular, and represents in this respect an interesting contrast with the discharge of the "tonic touch" unit shown in fig. 9.

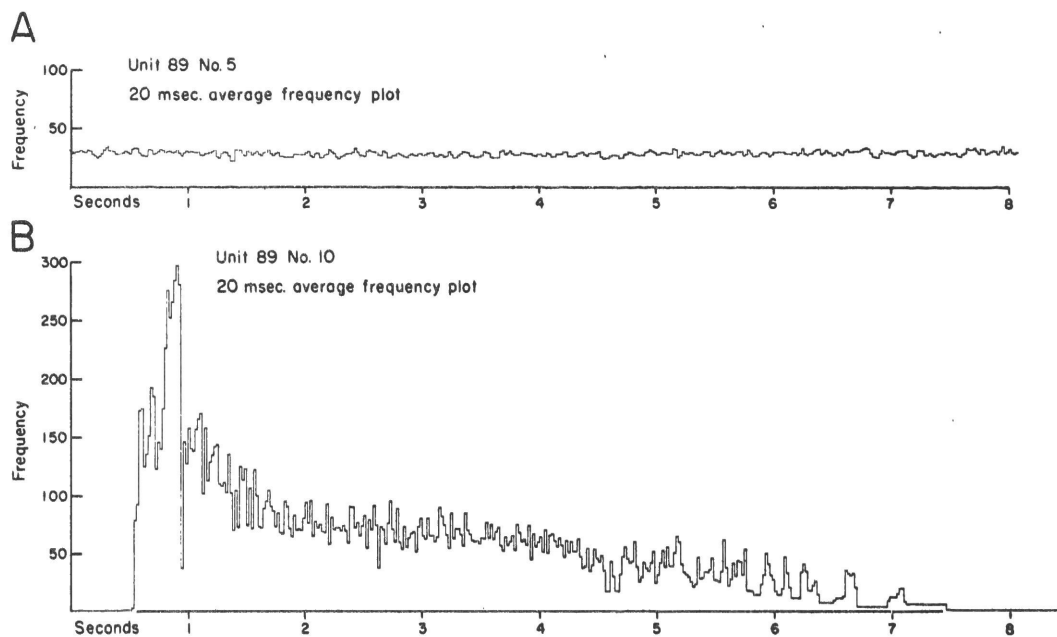


Fig. 18. Activity in a subcutaneous unit which responds to claw protrusion. Fig. 18A shows the response of this unit to the "firm" clip applied to the base of the claw. Fig. 18B shows the response of this unit to the "noxious" clip applied in the same way. The discharge in fig. 18A is clearly regular. In fig. 18B the activity is irregular and rapidly declines even though the "noxious" clip remains on the excitatory area. The unit could not be excited for sometime after removal of the "noxious" clip.

regularity of the discharge has been affected. After this stimulus the unit could not be excited for some time, but later there was partial recovery. Thus it would appear that at least this particular type of deep receptor behaves like the cutaneous units studied in the dorsal columns by showing inactivation following strong mechanical stimulation.

## II. Lateral Funicular Units

### A. Type I units

#### Location in the lateral funiculus

All type I units, which like all other units in the lateral funiculus can be assumed to be postsynaptic, have been found in a restricted region just beneath the dorsal root entry zone, as indicated in Fig. 2. There is evidence that fibers located in this region synapse in the lateral cervical nucleus (Brodal and Rexed 1953, van Beuskom 1955, Mark and Steiner 1958, McIntyre and Mark 1960, Lundberg and Oscarrson 1961, Norrsell and Voorhoeve 1962), a somatosensory relay nucleus whose axons, in turn, extend to that part of the thalamus which projects to the somatosensory cortex (Morin 1955, Morin and Catalano 1955, Bush 1961). While it has not been demonstrated that the fibers recorded from in these experiments actually reach the lateral cervical nucleus, it seems likely that at least some of them do.

#### General Properties

As has already been mentioned, all fibers which have been studied in the lateral funiculus, both type I and type II, have responded to more than one kind of cutaneous stimulation - mechanical stimuli, heating, and cooling, have all been effective. In addition, the fibers which constitute the input to lateral funicular units do not seem to be readily inactivated by strong mechanical stimulation and strong heating. A question of interest concerns whether different kinds of cutaneous stimuli evoke different and characteristic patterns of activity in these polymodal units. In this first section, consideration will be limited to type I fibers, and, as the responses of different type I units are quite similar, all illustrations except one will be taken from a single unit (unit 41). If different patterns of activity occur in a single fiber when different cutaneous stimuli are employed, the illustrations should show such differences.

### Responses to Mechanical stimulation

Figure 19 shows resting activity in a type I unit (unit 41).

Figure 19 shows an average frequency plot of this activity, where the averaging interval is 20 msec, and interval distribution histogram of the same activity is shown in 19B. It can be seen that the discharge was very irregular, and that intervals of many different sizes were present. It is especially noteworthy that though the overall frequency of the discharge was low, there were many short intervals. This has been typical of the resting activity recorded from type I units. Figure 20 shows the response of this same unit (unit 41) to a moving stimulator. In this case, the hair brush was slowly moved across the receptive field so as to engage only the hairs, a burst of activity occurring each time the hairs were touched. Figure 20A is again an average frequency plot and 20B is an interval distribution histogram of this response. It is evident that this sort of gentle mechanical stimulation was very effective in activating this unit. In fact, type I units have always been driven to higher frequencies by gentle discontinuous mechanical stimuli than by any other form of stimulation. Moving the hairs alone, as in Figure 20 has been effective in every case, though somewhat higher frequencies often result when both skin and hair are stimulated, suggesting that there may be some low threshold input that depends on direct stimulation of the skin. The responses require the presence of a moving stimulator, for if the stimulator becomes stationary the discharge soon declines to a much lower level. In general, type I units have a low threshold to movement and very slow mechanical stimulation is sufficient to cause a considerable response. Further increasing the velocity of stimulation increases the frequency of discharge somewhat, but type I units do not show striking velocity sensitivity, at least in the range of velocities where dorsal column units exhibit this effect. This can be seen by comparing Figure 20 with Figure 21, which shows the response of this unit (unit 41) to moving the hair brush rapidly across the receptive field.

A very reproducible feature of the behavior of type I units concerns the nature of their response to stimulators differing in texture. Figure 22 shows the response of another type I unit (unit 71) to the four stimulators which have been used previously to test the sensitivity of dorsal column units. A illustrates the response to the smooth disc. B, C, D show responses to discs covered with sandpaper of increasing coarseness. It is clear that the magnitude of the response was approximately similar in each case. This is in striking contrast to the behavior of dorsal column units, where the coarsest stimulator was always considerably



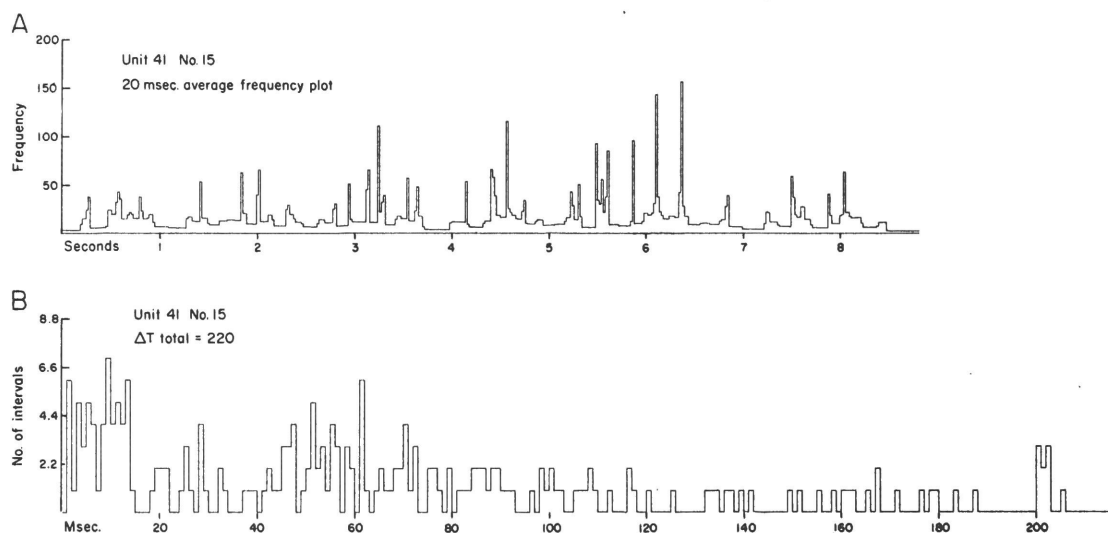


Fig. 19A. Resting activity in a type I lateral funicular unit (unit 41). The averaging interval is 20 msec. and the discharge is clearly irregular.

Fig. 19B. Interval distribution histogram of the resting activity, a portion of which is shown in fig. 19A. It can be seen that intervals of many different sizes are present, and that short intervals are well represented.

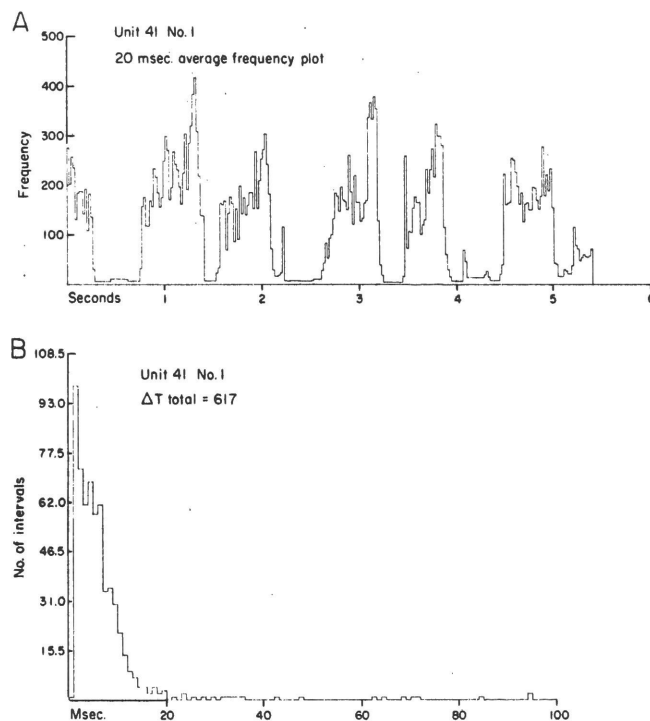


Fig. 20A. 20 msec. average frequency plot of activity in the type I unit illustrated in fig. 19 (unit 4I) as the hair brush is moved slowly across the receptive field several times in such a way that only the hairs covering the receptive field are touched. This slow, gentle stimulus activated the unit very effectively.

Fig. 20B. Interval distribution histogram of the activity shown in fig. 19A.

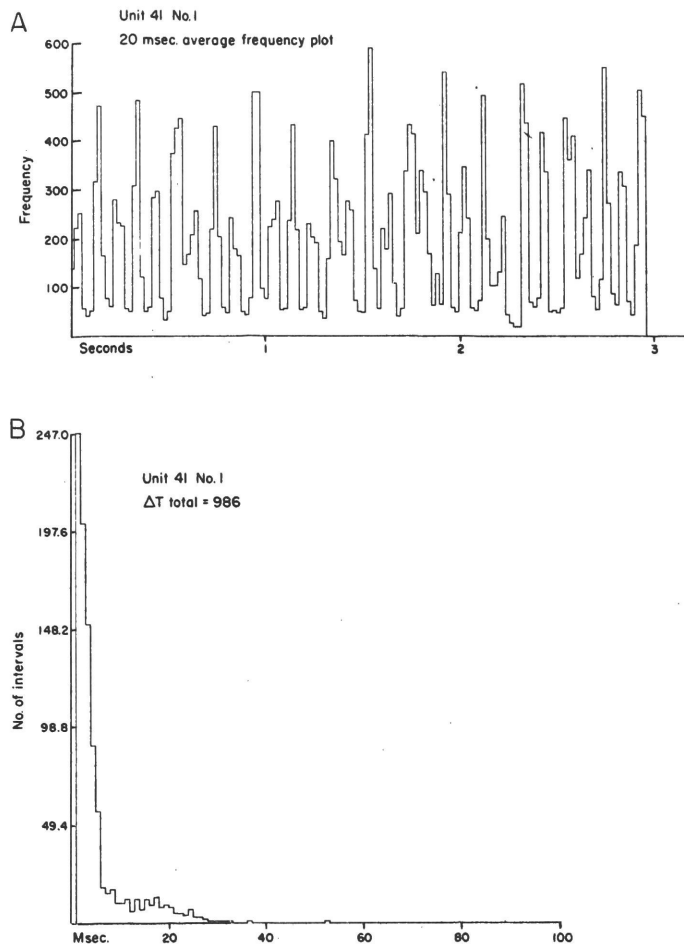


Fig. 21A. As in fig. 20A, but here the hair brush is being moved rapidly across the receptive field. The stimulator is also being applied more frequently than in fig. 20A.

Fig. 21B. Interval distribution histogram of the activity shown in fig. 21A.

more effective than the smoothest. This observation suggests that at least some of the mechano-sensitive peripheral fibers which activate type I lateral column units have properties which differ from those exhibited by primary afferents in the dorsal columns.

Type I units also showed a maintained discharge in response to steady deformation of the skin. The overall nature of the response to the "firm" clip in unit 41 is shown in Figure 23, where the discharge has been averaged over intervals of 0.5 sec. The first arrow indicates approximately when the clip was applied. There was an initial comparatively high frequency response during application of the clip due to movement of the skin and hair, and there was another similarly induced period of increased discharge during removal of the clip (second arrow). Clip removal was followed by an after discharge. It is clear that a well maintained discharge occurred while the clip was causing an apparently steady deformation of the skin. As shown in more detail in Fig. 24, the maintained discharge was rather irregular, though the interval distribution histogram in B shows that a much smaller range of interval sizes was present during this response than occurred during resting activity. It is interesting to note that relatively few short intervals are present during the maintained response to the "firm" clip.

Figure 25 shows the response of this same unit (unit 41) to the "noxious" clip. 25A shows the transiently elevated discharge that occurred during clip application, as a result of moving the skin and hair (the clip was applied at the arrow), and this then declined to a maintained response which in this unit was of a higher frequency than the maintained response to the "firm" clip. The interval distribution histogram in Figure 25B resembles that given by the "firm" clip except that the curve as a whole is shifted to the left with the result that more short intervals are present. This was only one of the variety of responses exhibited by type I units as the mechanical stimulus increased from "firm" to "noxious". The most usual finding was that the responses to the "firm" and "noxious" clips were of about equal magnitude. In some cases the response to the "noxious" clip was actually of lower frequency than the response to the "firm" clip. Thus there was no typical change in the level of discharge of type I units as mechanical stimulation increased from "firm" to "noxious". It should be noted that regardless of the level of the response to the noxious clip, this response was well maintained, indicating that the receptors producing it were not being inactivated.

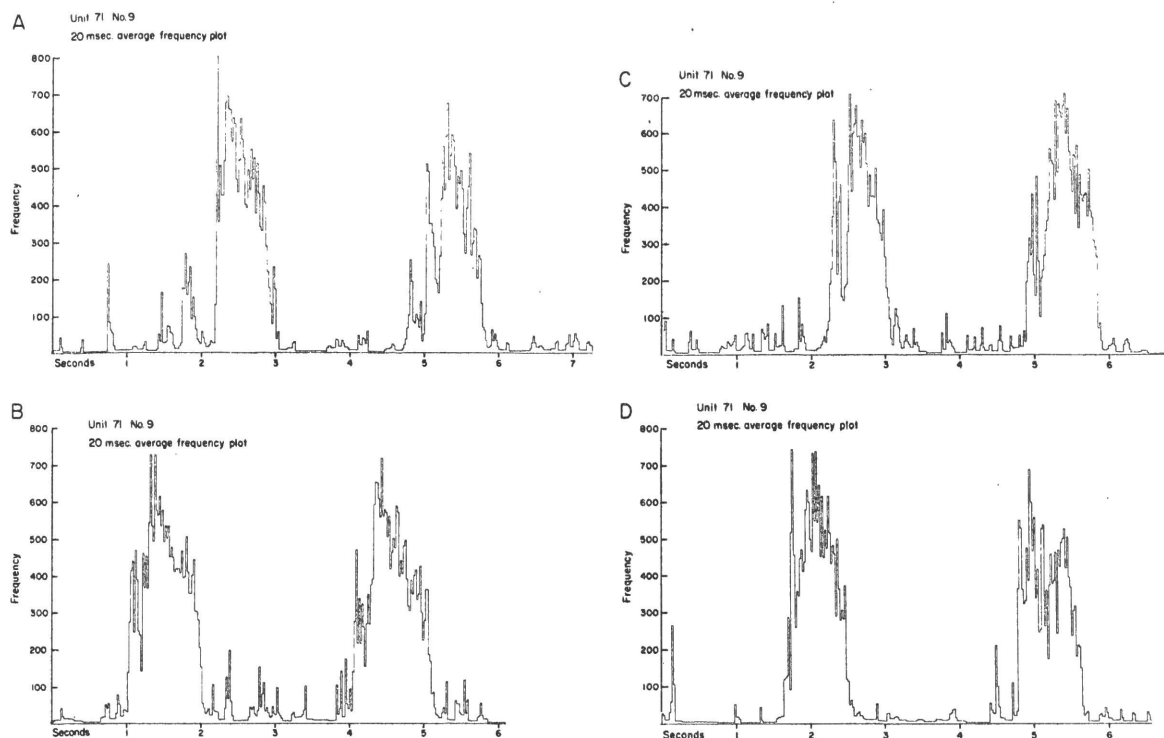


Fig. 22. The response of another type I unit (unit 71) to moving stimulators of different texture across the receptive field. Fig. 22A shows the response to the smooth stimulator, figures 22B, 22C and 22D to stimulators covered with sandpaper of increasing coarseness. Each of the stimulators seems about equally effective in activating the unit.

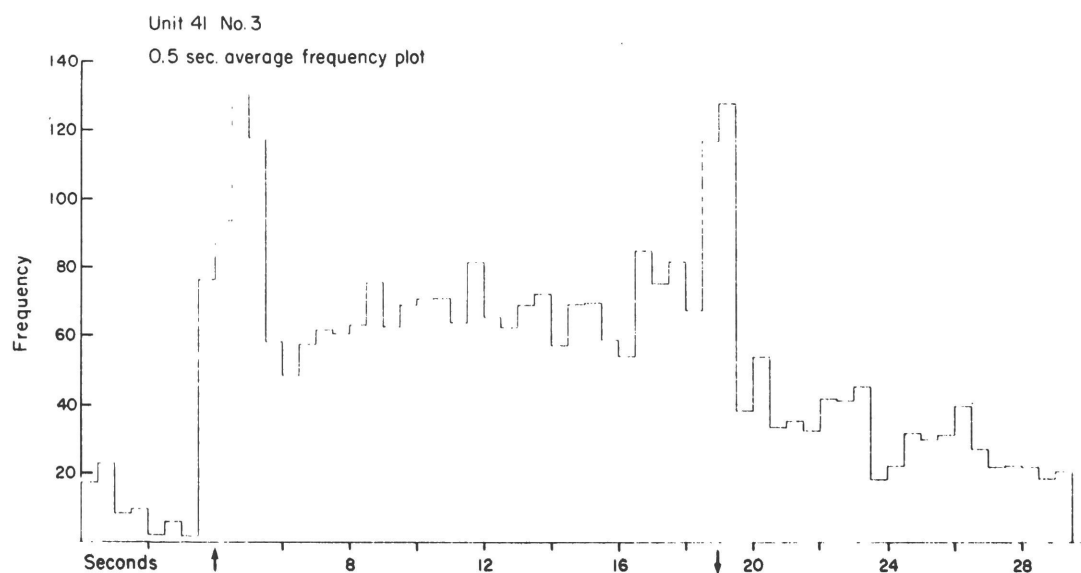


Fig. 23. The response of the type I unit shown in figures 19, 20 and 21 (unit 41) to "firm" pressure. Here the frequency has been averaged over a 0.5 sec. interval to show the overall features of the response. The "firm" pressure clip was applied at the first arrow and removed at the second arrow. A considerable increase in activity occurs during application and removal of the clip, but there is also a well maintained response while the clip is "steadily" compressing the skin. An after-discharge followed removal of the clip.

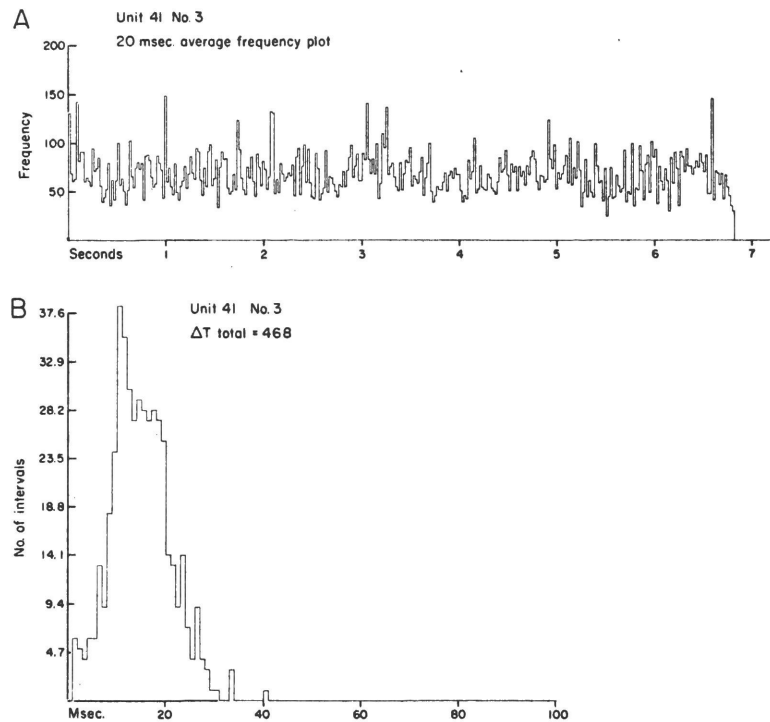


Fig. 24A. Illustrated here is a portion of the response to "steady" pressure shown in fig. 22.

Fig. 24B. An interval distribution histogram of the discharge shown in fig. 24A. It is interesting that relatively few short intervals occur during this response.

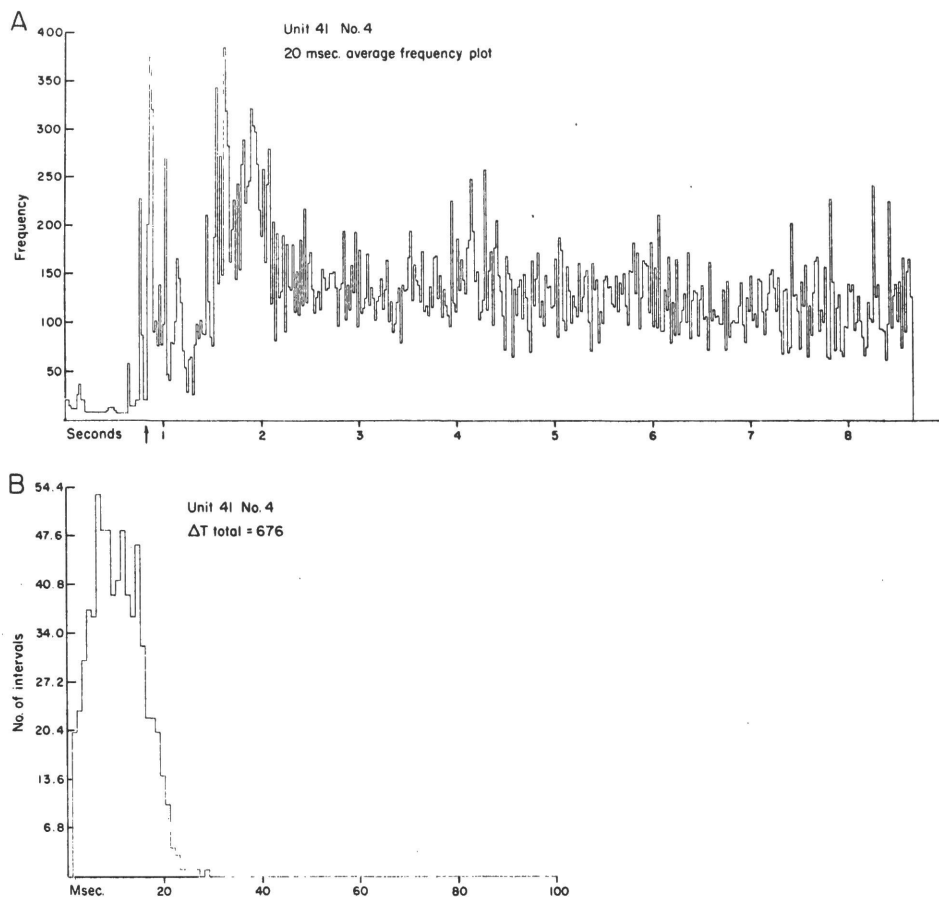


Fig. 25A. Response of the same type I unit (unit 41) to "noxious" pressure. The "noxious" clip was applied at the arrow, causing the usual comparatively high frequency discharge due to movement of the skin and hair. A well maintained and quite irregular response continues after the clip becomes "steady".

Fig. 25B. Interval distribution histogram of maintained activity in response to the "noxious" clip. The curve resembles that given by "firm" pressure except that it is shifted to the left, and thus more short intervals are present.



Figure 26 shows an interesting feature of the behavior of type I units. Illustrated here is the after-discharge which followed removal of the noxious clip. Directing attention to the frequency plot in A, it can be seen that the after-discharge was irregular, and that at a certain point the frequency reached a very high level for a short time. An examination of this response interval by interval shows that a high frequency burst of impulses was responsible for this transient very high frequency component of the response, and that other shorter bursts also occurred. The interval distribution histogram in Figure 26B shows that there were an unusually large number of very short intervals during the response, these being intervals making up the bursts. It has been a general observation that type I units do under some circumstances discharge in a bursting fashion, and since this represents a change from the usual pattern of evoked discharge in these units, bursting activity could perhaps convey a different kind of information than that conveyed by a non-bursting discharge. It will be of interest in this connection to determine whether bursting characteristically occurs in response to any particular kind of cutaneous stimulation. This matter will be considered further after illustrating the responses in this same type I unit (unit 41) to thermal stimuli. The maintained responses in this unit to both the "firm" and "noxious" clips were of the non-bursting type.

#### Responses to Thermal Stimuli

##### A. Cooling

Figure 27 shows the response of unit 41 to cooling the receptive field with ethyl chloride. The ethyl chloride was applied a few seconds before the beginning of Figure 27. The response was quite well maintained, and of reasonably high frequency. The frequency plot in 27A shows that the discharge was more irregular than the response to the "firm" clip, with certain transient increases in frequency which suggest that some bursts may have been present. A more detailed interval by interval analysis of this response indicates that some bursts did occur, and the interval distribution histogram in 27B shows that short intervals were present. Type I units have, in all cases tested, responded to ethyl chloride with an increase in activity. In some cases this increase has been relatively transient, in others quite prolonged. In the absence of accurate measurements of skin temperature it is difficult to know whether these differences in response are related to differences in the nature of the stimulus or to differences in the sensitivity of the receptors.

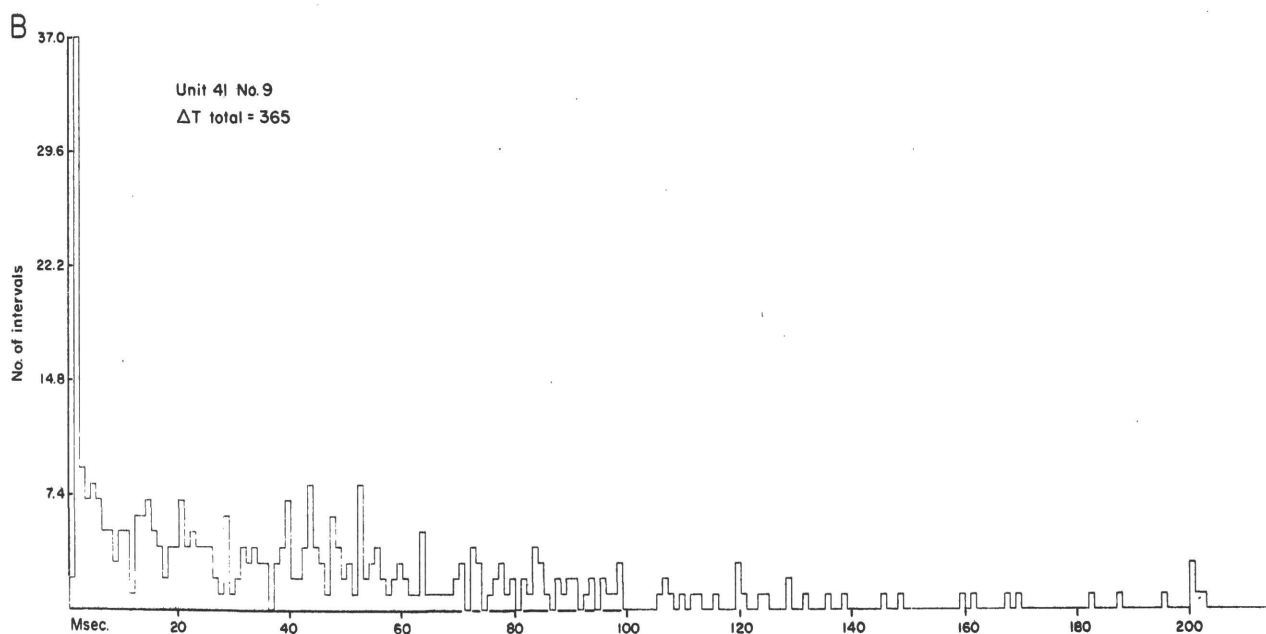
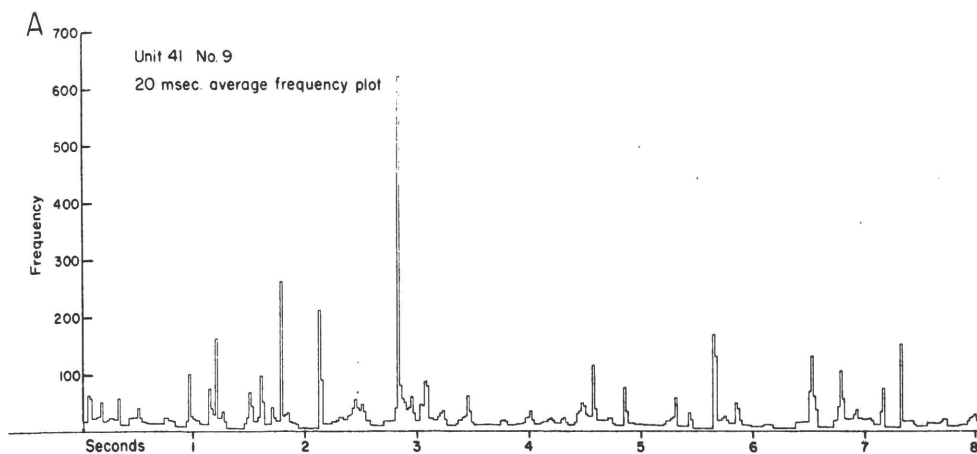


Fig. 26A. After-discharge in the same type I unit following removal of the "noxious" clip. The activity is very irregular, with the frequency at one point reaching a very high value for a short time. A high frequency burst of action potentials occurred at this point. Fig. 26B. Interval distribution histogram of the activity shown in fig. 26A. Many very short intervals are present due to a tendency for high frequency bursts of activity to occur.

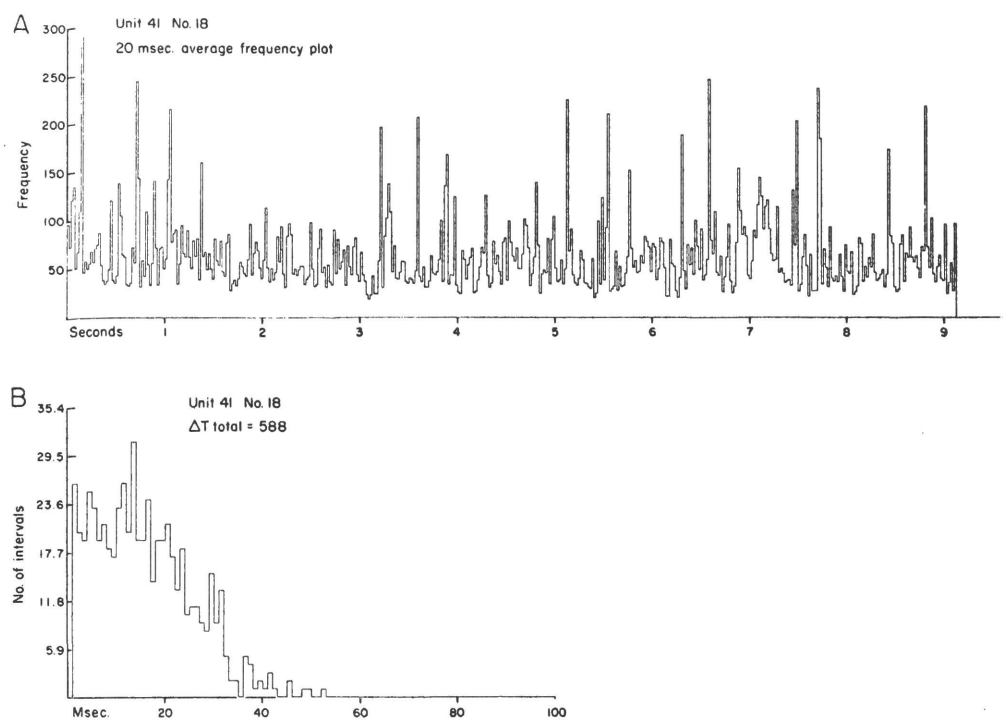


Fig. 27A. Response of the same type I unit to cooling with ethyl chloride. The ethyl chloride was applied a few seconds before. An irregular response occurs with some bursting.

Fig. 27B. Interval distribution histogram of the activity shown in fig. 27A. In this discharge short intervals are well represented.

Attempts were also made to activate type I units by thermode cooling. Running ice water into a thermode placed on the dampened skin caused little or no activation, even though final temperatures were often as low as  $12^{\circ}\text{C}$ . This result was puzzling in view of the ease with which the units were activated by ethyl chloride. Two explanations for the difference between ethyl chloride and thermode cooling were considered: 1. Ethyl chloride cooling was more rapid than that which occurred when ice water was run into the thermode, and the latter was insufficiently rapid to cause a discharge. 2. Ethyl chloride acted as some sort of complex stimulus causing not only cooling but other effects which were in fact responsible for the activation of type I units. In order to test which of these alternatives was correct, measurements were made of the rate of skin cooling caused by ethyl chloride, and in addition, attempts were made to achieve rapid thermode cooling by circulating dry ice cooled acetone through the thermode. Measurements of skin surface temperatures after application of ethyl chloride showed that this stimulator did in fact cause a very rapid fall in temperature, considerably more rapid than the fall caused by circulating ice water through the thermode applied to the skin. Though only a few type I units have been examined during stimulation of the receptive field with a thermode carrying dry ice cooled acetone, all these units responded. The discharge was transient and occurred only while the receptive field was actually being cooled. Final temperatures in these cases were routinely below  $0^{\circ}\text{C}$ ., and the thermode was frozen to the skin. Thus it would seem that type I units are able to respond to cooling, if this is sufficiently rapid. Whether this response is secondary to mechanical changes in the skin occurring during cooling is difficult to determine. Whatever the mechanism may be, it is clear that very rapid changes in temperature are required, and it is difficult to imagine many situations in nature where sufficiently rapid changes in temperature might occur.

#### B. Heating

Figure 28 shows the response of this same unit (unit 41) to thermode heating. Again the discharge is irregular. The interval distribution histogram in 28B shows that short intervals were present, but an interval by interval analysis of this response failed to disclose any bursts. The response was well maintained, and this has been typical of type I units, even though skin temperatures in excess of  $50^{\circ}\text{C}$  have occurred for some time during stimulation. Also, type I units have been observed to respond to repeated heating of the skin to temperatures in excess of  $50^{\circ}\text{C}$ , even though the skin may previously have been frozen with dry ice cooled

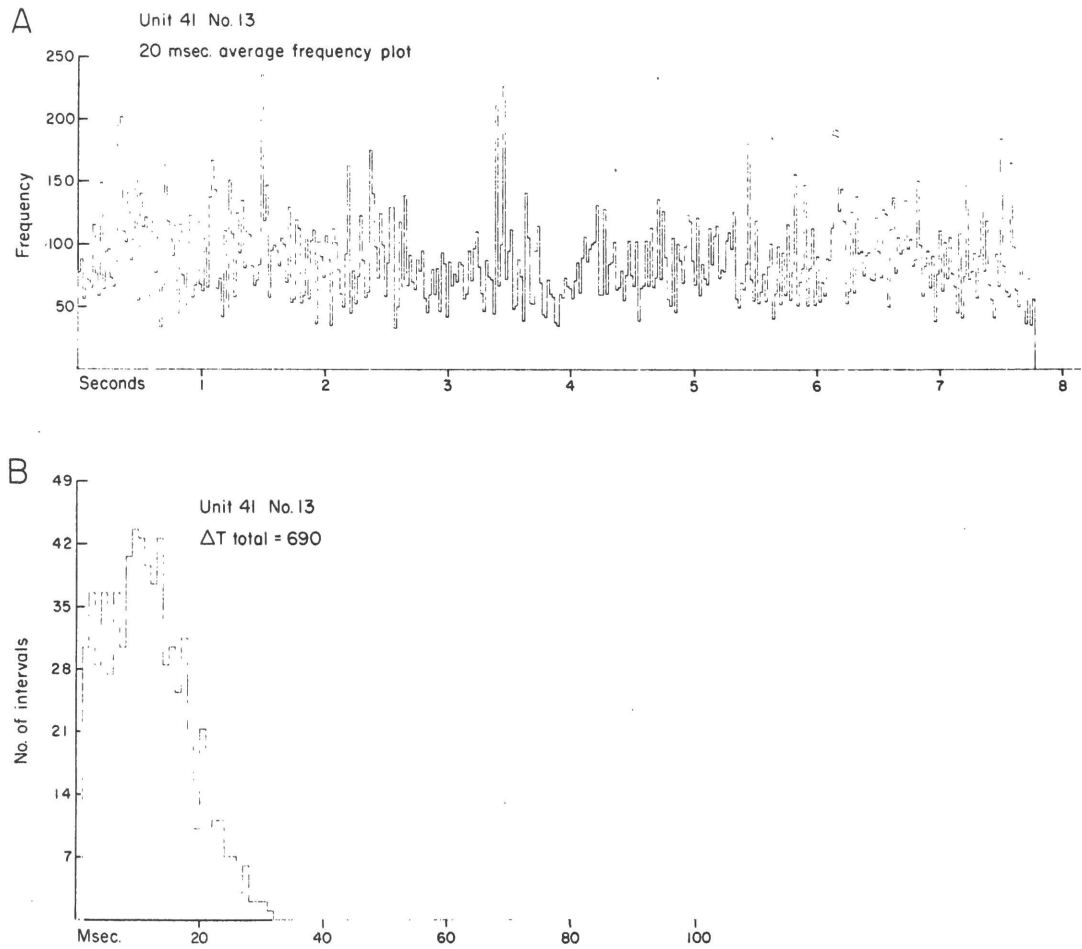


Fig. 28A. The response of the same type I unit to "noxious" heat. The response is quite irregular, but an examination of the discharge interval by interval showed that bursts were not prominent.

Fig. 28B. Interval distribution histogram of the activity shown in fig. 28A. As in the response to cooling, short intervals are well represented.

acetone. Observations of this type indicate that the peripheral receptors responding to heating, like those responding to strong mechanical stimulation, are not readily inactivated by the strong stimuli which excite them. In addition, it has been noted that areas of skin subjected to strong mechanical stimuli and strong heating show virtually undiminished sensitivity to gentle mechanical stimulation. This contrasts with the situation in the dorsal columns, where units were typically inactivated by strong stimulation, and again suggests that at least some of the mechano-sensitive peripheral fibers which activate lateral column units have properties which differ from those possessed by primary afferents in the dorsal columns.

The response of type I units to heating does not begin as soon as the temperature starts to increase, but only after some delay. If the temperature is elevated slowly the response can be seen to begin very abruptly as the temperature reaches a certain value. This threshold temperature is characteristic of the particular unit, and for all type I units has been found to lie between  $44^{\circ}\text{C}$  and  $46^{\circ}\text{C}$ . Until this threshold temperature is reached there is no increase in activity, even though the initial temperature may be as low as  $25^{\circ}\text{C}$ . If, however, the temperature is increased rapidly some units have shown an increase in activity at  $38^{\circ}\text{C}$  -  $40^{\circ}\text{C}$ , or even lower. It is not certain whether this represents a genuine response at a temperature lower than  $44^{\circ}\text{C}$ , or whether the temperature of the thermistor is lagging behind the temperature of at least some part of the skin. The latter alternative is not unlikely. In view of the fact that the depth of the receptors is unknown, a slow increase in temperature has the additional advantage that under such circumstances the increased surface temperature is more likely to accurately reflect the true temperature of the receptors. In any case, it appears that any very significant activation of type I units requires temperatures that evoke pain in man. It is interesting that the threshold temperature for activation of these units during a slow increase in temperature is the same as the temperature at which thermal pain begins in man.

#### Patterns of Activity

Type I units are capable of producing both bursting and non-bursting types of discharge. Certain kinds of cutaneous stimuli seem to favor the appearance of bursting activity; both cooling and heating the skin have produced this type of discharge. Equally often however bursting did not occur during activity resulting from thermal stimuli. Maintained mechanical deformation of

the skin has generally not been effective in producing a bursting discharge, though the "mild" clip has in some instances caused this sort of activity. In general, bursting activity does not seem to occur if the overall frequency of a maintained discharge is high. For example, the initial response to strong heating of the skin may be of fairly high frequency, and at this time no bursts are present, but as the skin cools somewhat after the hot water has been turned out of the thermode the discharge falls to a lower level, and now bursting occurs. In fact, the only circumstance in which a bursting discharge has routinely been seen is during the after discharge which almost always follows removal of the "noxious" clip. After discharge has also been seen after removal of the "firm" clip, but is generally of lower frequency and less bursting than the after discharge which follows the "noxious" clip. It should be noted that even the strongest after discharges have been of relatively low frequency compared to the response occurring during maintained "firm" or "noxious" mechanical deformation, or strong heating. It would seem, therefore, that a bursting type of discharge is not reproducibly associated with any particular kind of cutaneous stimulation.

Type I units can be best activated by gentle discontinuous mechanical stimulation of the skin and hair. The units are driven so strongly that a bursting type of discharge can be produced by this type of stimulation, if it is appropriately applied. For example, rapid displacement of the hairs has been observed to produce discreet bursts, and a puff of air delivered to the unclipped receptive field causes this type of discharge. In fact, by appropriate manipulation of gentle cutaneous stimuli it should be possible to produce a variety of patterns of discharge in these units. This fact would again make it difficult to associate any particular pattern of activity in type I units with a particular modality of cutaneous sensation.

#### Receptive fields

All type I units have been activated from ipsilateral receptive fields. The sizes of these fields, as determined with gentle discontinuous mechanical stimuli, have varied somewhat, and there has been some tendency for the smallest fields to be located distally. A typical distal receptive field might include the two most lateral toes (both hairy and pad skin) and the adjacent part of the foot, the proximal margin being such that the field occupied the distal third of the lateral part of the foot. Fields which were located more proximally on the limb or on the tail were generally somewhat larger, but the difference in size between proximal and distal fields has not been so striking as in the dorsal

column "hair" units. Also, there are indications that the size of the receptive field depends on the kind of stimulation employed in mapping it. If a moving stimulator is used the receptive area is often larger than that which can be obtained if only the response to steady displacement of the skin is considered. In fact, some units have exhibited the usual low threshold activation by a moving stimulator, but have shown little or no response to maintained deformation of the skin. This suggests that the receptors mediating the response to gentle discontinuous mechanical stimulation are at least in part separate from those that are activated by maintained deformation of the skin. Units with such properties can be activated by cooling the skin with ethyl chloride, but in the cases tested they have shown no response to heating. This suggests that the receptors which respond to heating are to some extent separate from those which respond to ethyl chloride and those which respond to a moving stimulator. Whether the receptors responding to heating are the same as those responding to maintained mechanical deformation is not known.

Most of type I units, but not all, could be inhibited by stimulating certain areas. Inhibition was detected as a reduction in either spontaneous or evoked activity. Stimulation of the contralateral toes was generally most effective in producing inhibition, regardless of whether the excitatory receptive field was on the ipsilateral foot or on the tail. In some cases inhibition could also be obtained by stimulating areas adjacent to the excitatory receptive field. For the most part, mechanical stimuli have been employed in eliciting inhibition, and strong stimulation has usually been required. Little information is available concerning the inhibitory effectiveness of thermal stimuli. It should be noted that although the activity of type I units can be inhibited, the effects are not powerful. The impression obtained is of a rather weak inhibition which requires strong stimulation if it is to be seen at all.

#### Summary of type I units

Type I units typically show a low level irregular spontaneous discharge, the average frequency usually being of the order of 10/sec. The units are best driven by a moving mechanical stimulator which gently displaces both the skin and hair, and they are well activated by a slight movement of the stimulator. They show some velocity sensitivity within the range of velocities used in this study, but this effect is not nearly so marked as in the dorsal column units. Furthermore, the units respond equally well to smooth and coarse stimulators. The units respond to maintained mechanical deformation with a maintained dis-



charge, and while "noxious" pressure does not necessarily evoke a larger discharge than "firm" pressure, "firm" pressure usually causes a larger response than does "mild". After discharge has been observed following removal of the "mild", "firm", and "noxious" clips. The "noxious" clip has generally been the most effective in producing an after discharge. A transient response occurs when the skin is cooled, if the temperature falls rapidly enough. In fact, a very rapid rate of cooling is required to evoke a discharge. Little or no response occurs to maintained low temperatures. Heating the skin to temperatures above 44°C or 45°C causes a well maintained discharge which lasts as long as the temperature remains elevated. The receptors responsible for the response to a moving stimulator, to maintained mechanical deformation, and to strong heating are not readily inactivated by damaging stimuli. The units display both bursting and a non-bursting patterns of discharge, but these can not be correlated with any particular kind of cutaneous stimulation. Gentle mechanical stimuli when properly applied can cause bursts as well as various other patterns of activity. Receptive fields are of intermediate size, and all are ipsilateral.

#### B. Type II Units

##### Location in the lateral funiculus

Type II units have also been found in the dorsal half of the lateral funiculus, but ventral to the region where the type I units are located (see Figure 2). Recordings have been made from type II units over a comparatively wide area in the lateral funiculus, and they contrast in this respect with type I units, which were found in a fairly restricted region. In general, type II units do not form as homogeneous a group as do type I units. It should be noted that in addition to the fibers which project to the lateral cervical nucleus, other fibers in the lateral funiculus are known to project to the reticular formation and thalamus (Mehler, Feferman, and Nauta 1960) and to the cerebellum (Oscarsson 1957). Whether spinoreticular fibers mediate sensory information which reaches consciousness is not known; spinocerebellar fibers probably do not, since cerebellar lesions do not interfere with somatic sensations in man. The actual destination of the type II fibers studied in these experiments is not known.

##### General properties

Figure 29 shows resting activity in a type II unit. In 29A the activity has been averaged over 0.5 sec. intervals and presented as a frequency plot. It can be seen that the resting discharge was of considerable magnitude in this unit. Resting discharge has been seen in most type II units, though certain units have

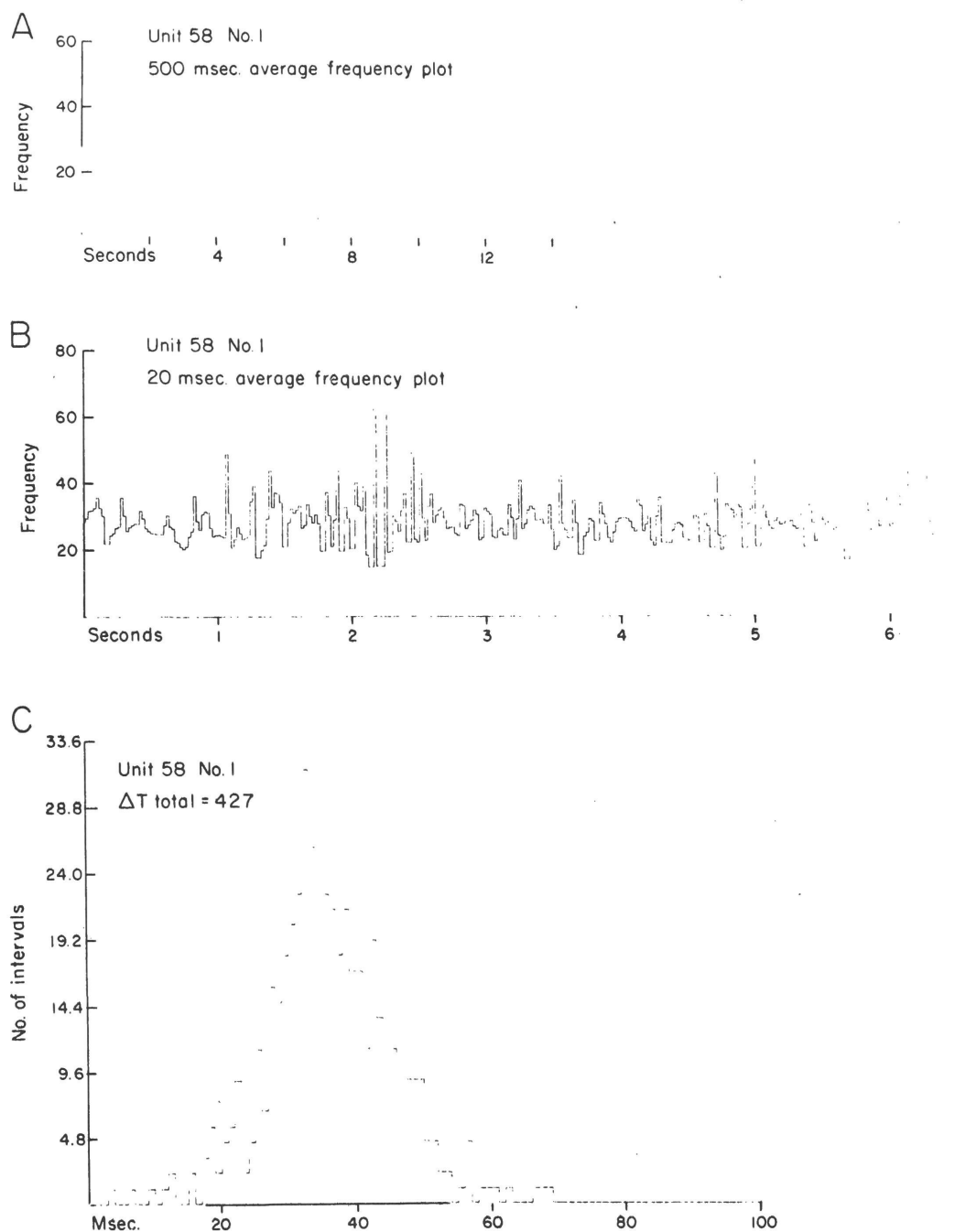


Fig. 29A. Resting activity in a type II lateral funicular unit. The frequency has been averaged over an interval of 0.5 sec., and the discharge appears quite steady.

Fig. 29B. A plot of the same activity shown in fig. 29A, but here the averaging interval is 20 msec. The discharge can be seen to be comparatively irregular when examined with a short averaging interval.

Fig. 29C. Interval distribution histogram of the activity shown in fig. 29A. Short intervals are virtually absent. This absence of  $\Delta T$  distinguishes type II units from type I units.

have shown no resting activity whatever. Figure 29A also shows that this activity, when averaged over 0.5 sec. intervals was quite constant. 29B shows another frequency plot of the same discharge, but here the averaging interval is 20 msec., and it is evident from this graph that the discharge was actually quite irregular, even though the frequency averaged over longer intervals was reasonably steady. Figure 29C shows an interval distribution histogram of the resting activity, showing that though the range of intervals present was actually quite large, no short intervals occurred. This has been a consistent finding with respect to type II units; no matter how they are activated, these units do not respond with short intervals. In this they differ markedly from type I units.

Type III units have been found to respond to a variety of cutaneous stimuli, and also to stimulating structures deep to the skin. Gentle discontinuous mechanical stimulation of the skin has been effective in activating them to some extent, but they are much less sensitive to this kind of stimulation than type I units. The response to a moving stimulator is not appreciably better than the response to steady mechanical displacement, and, in general, it is necessary to apply somewhat stronger mechanical stimuli to the skin if type II units are to be well activated. The "mild" clip characteristically produces little response, while the "firm" and "noxious" clips are usually about equally effective. Figure 30 illustrates the response of the same type II unit shown in Figure 29 to application of the "firm" clip. The clip was applied before the record began and only the response to "steady" deformation is shown. Figure 30A shows the discharge averaged over intervals of 0.5 sec. Figure 30B shows a portion of this same discharge, but here the averaging interval is 20 msec. Figure 30C is an interval distribution histogram of the activity shown in Figure 30A, and it can be seen that no short intervals were present, and that the discharge was reasonably regular. Like type I fibers, the units respond to ethyl chloride cooling, but showed little response to thermode cooling when ice water was circulated. Type II units have not been studied during thermode cooling with dry ice cooled acetone. Units of this type also respond to heating, though the temperature at which activity begins has not been very clearly defined. There is some evidence that increased activity may begin when the skin surface temperature reaches values between 35°C and 40°C. It has always been found that a persistent discharge occurs when the temperature of the skin surface exceeds 44°C - 46°C.

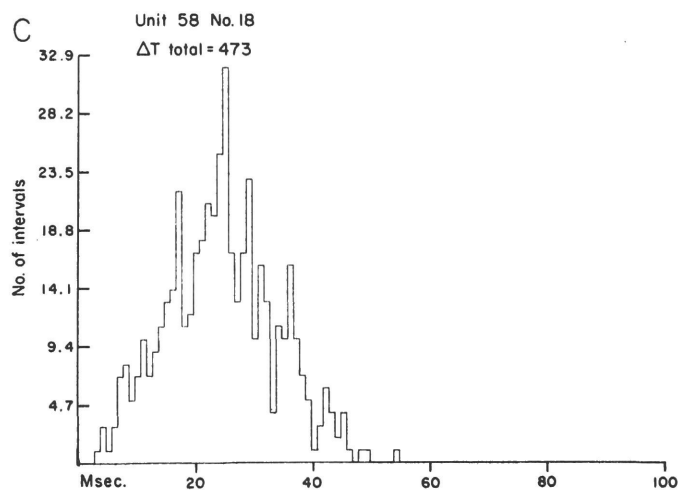
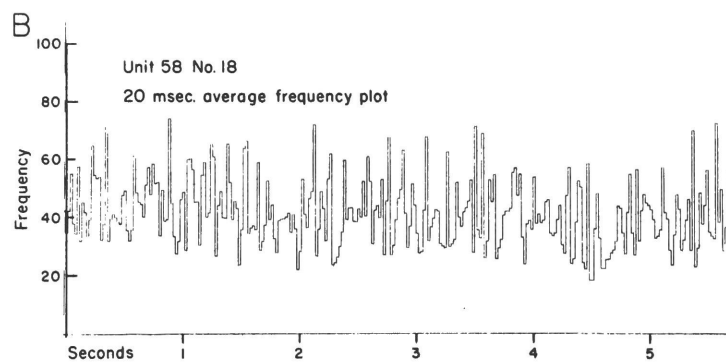
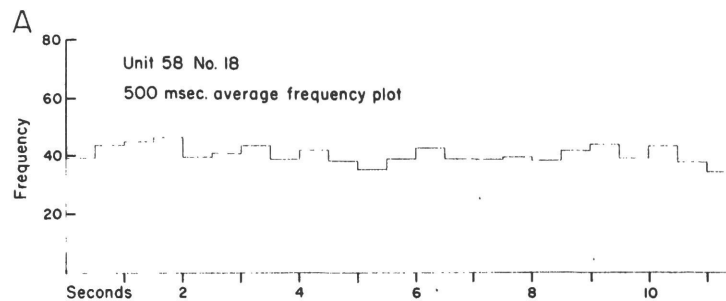


Fig. 30A. Overall response of the type II unit shown in fig. 29 to application of the "firm" clip. Only the response to "steady" deformation is shown.

Fig. 30B. A more detailed examination of a portion of the response shown in fig. 30A.

Fig. 30C. Interval distribution histogram of the activity shown in fig. 30A. It can be seen that no short intervals are present, and that the discharge is reasonably regular.

Typically, type II units are about equally well driven by the different thermal and mechanical stimuli which activate them. As in the case of type I units, the peripheral receptors activating type II units do not seem readily inactivated by strong mechanical and strong thermal stimuli. In no instance has it been possible to detect any characteristic pattern of discharge in type II units which depends on the nature of the stimulus, and these units do not discharge in a bursting fashion. Sometimes a particular stimulus appeared to produce both excitation and inhibition concurrently, and in such cases rather complicated patterns of activity could occur. However, repetition of the stimulus usually caused a quite different pattern of discharge. If a comparison is made between the pattern of activity seen in type I units as a whole and that seen in type II units as a whole, striking differences are apparent. But these differences are associated with the properties of the post-synaptic element and not the nature of the activating stimulus.

#### Receptive fields

Type II units have typically exhibited large and complex receptive fields. Inhibitory influences have been prominent, and often a mixture of excitatory and inhibitory effects seemed to result from stimulating the same spot. Figure 31 shows inhibition of the type II unit illustrated earlier, without any visible concomitant excitation. The inhibition in this case was of the resting discharge and was caused by application of the "firm" clip, the duration of the application being shown by the arrows in Figure 31A. The first part of the response shown in Figure 31A is illustrated in greater detail in Figure 31B, where the activity has been averaged over intervals of 20 milliseconds. It can be seen that the inhibition was well maintained and reasonably powerful, as has been characteristic of type II units. It was not uncommon to find type II units completely silenced by appropriate inhibitory stimuli. In some of these units the receptive field determined with one kind of cutaneous stimulation differed considerably from that obtained when another kind of stimulation was used. As determined with moderate mechanical stimuli, excitatory receptive fields have been seen which include most of both hind limbs and the tail. In other units the excitatory field has been quite small, with extensive bilateral areas producing inhibition. As can be seen, the receptive field organization in these units is quite different from that possessed by type I units. It has been observed often when studying type II units that gentle or moderate mechanical stimulation of one part of the receptive field may cause excitation, whereas strong mechanical stimulation of the same spot will cause inhibition. Thus, in

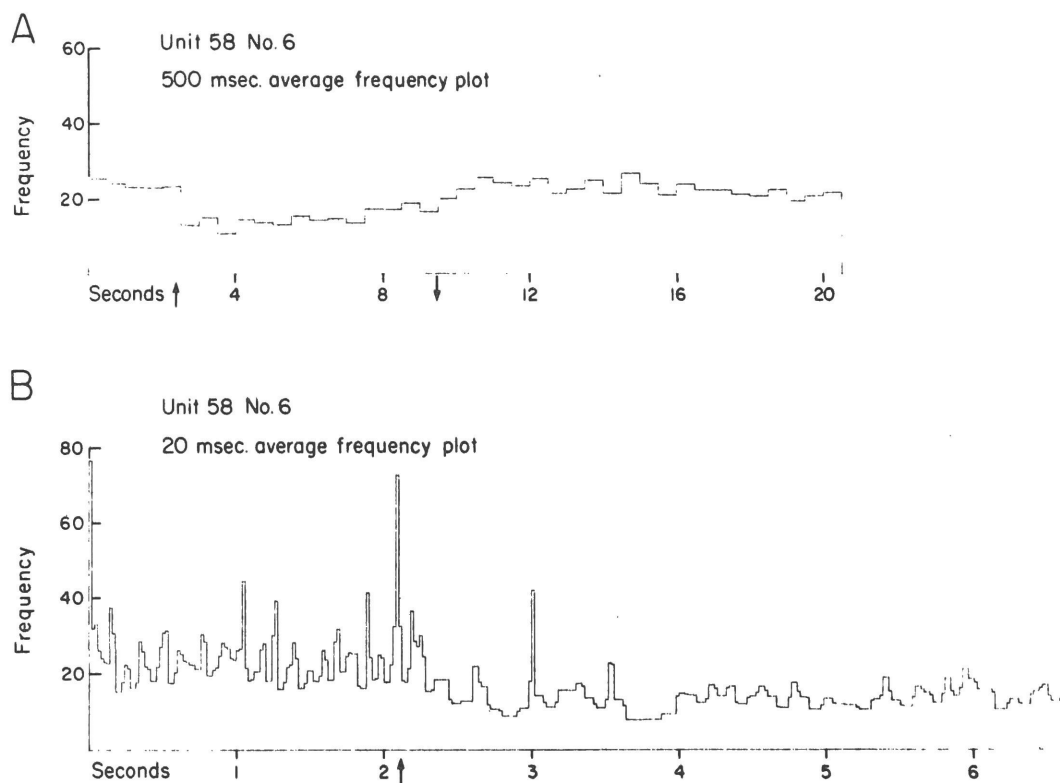


Fig. 31A. Overall response of the type II unit illustrated earlier to an inhibitory stimulus, in this case the "firm" clip. The arrows indicate when the clip was applied and removed. The inhibition is quite well maintained and reasonably strong.

Fig. 31B. The first part of fig. 31A shown in greater detail.

some units the excitatory field as mapped with moderate mechanical stimuli has been larger than the excitatory field determined with strong mechanical stimuli, due to the presence of inhibition from some areas when the latter type of stimulation was applied. However, other units have shown just the opposite behavior, the excitatory field being larger when strong mechanical stimulation was employed, because gentle mechanical stimuli produced inhibition from more extensive areas than strong stimuli. It is of interest to determine the effects of applying thermal stimuli in such cases. Only strong heating has been properly studied in this connection, and it has usually been found that strong heating applied to a particular area produced the same effect whether excitatory or inhibitory, as strong mechanical stimulation. However, there have been instances in which effects of opposite sign have been obtained in response to strong mechanical stimulation and strong heating of the same site. Such observations are most easily explained by assuming that different peripheral receptors are stimulated by strong heating and by strong mechanical stimulation, but other interpretations are also possible.

#### Summary of type II units

Type II units often show fairly high levels of resting discharge. They can be activated by mechanical stimulation of skin and subcutaneous tissues, and by heating or cooling the skin, and all these stimuli produce a roughly comparable discharge. The response to a moving mechanical stimulator is not much greater than the response to steady mechanical deformation of the skin. Gentle mechanical stimuli are less effective in activating these units than moderate or "firm" stimuli, but "noxious" mechanical stimulation is not typically better than "firm". The units have a typical pattern of discharge which is comparatively regular and does not contain short intervals. A pattern of this type is seen regardless of the nature of the stimulus. Receptive fields are large and complex, with different kinds of stimuli sometimes producing effects of opposite sign when applied to the same site. Inhibitory influences are generally much more prominent than in type I units.

#### Overall Comparison of Dorsal Column and Lateral Funicular Units

Dorsal column units appear best suited for conveying information about mechanical events at the body surface, especially movement of the skin. Rapidly adapting units seem very specific in this regard. Slowly adapting dorsal column units could possibly convey some sort of crude information regarding cooling of the skin, but, in general, the mechanical properties of this system seem the most highly evolved, perhaps allowing some texture discrimination. Such data support the usual ideas about the function of the dorsal columns (Rose and

Mountcastle 1959).

Single lateral column units have been found to be activated by more than one kind of cutaneous stimulation. Mechanical stimulation, strong heating and rapid cooling have all been effective. Characteristic and reproducible patterns of activity which depend in some obvious way on the type of stimulation employed have not been found. Lateral column units have shown less tendency than dorsal column units to be inactivated by strong stimulation. In general, the most striking differences in the patterns of discharge observed in the lateral columns have been between different units, and have seemed to be characteristic of the unit and not of the type of stimulation used to activate it.



## Discussion

The present experiments have been concerned with activity recorded from single units at the spinal level in response to various kinds of cutaneous stimuli. In the discussion which follows consideration first will be given to the relationship of the data derived from these present experiments to data from other closely related investigations, and this will be followed by a brief consideration of work concerned with somatic sensations carried out at supraspinal levels. The basic question posed in the present investigation, namely, whether single sensory neurons respond to stimuli related to a single or more than one modality of cutaneous sensation, can be answered most fully for primary afferent fibers. Much work at supraspinal levels has been characterized by the use of rather poorly controlled stimuli, often related to only one cutaneous modality.

### I. Dorsal Column Units

#### A. "Hair" Units

Units which could be effectively activated by hair movement were early described by Adrian (1931). Recording from peripheral nerve fibers innervating the skin of the guinea pig, he noted that the discharge initiated by hair movement was rapidly adapting, and that single hair receptors would follow repetitive stimulation at frequencies of several hundred per second. The latter observation was considered to have important theoretical implications. Since such high frequency stimulation of the hairs of an intact guinea pig did not appear to cause pain, Adrian concluded that pain does not result simply from excessive activation of low threshold mechano-sensitive receptors, and that there are probably other fibers which mediated pain specifically. In their study of single dorsal root fibers innervating the skin of the cat, Hunt and McIntyre (1960) also described "hair" units, that is units which could be as well activated by hair movement alone as by stimulation of skin and hair together. In agreement with Adrian they found these receptors to be rapidly adapting, and in addition showed that they were not responsive to thermal stimuli. Witt and Hensel (1959) had also noted that rapidly adapting cutaneous receptors in the cat were not activated by thermal stimuli. Using a vibrator having a sinusoidal input, Hunt and McIntyre were unable to produce very high frequency following in "hair" units. This contrasts with Adrian's findings and the results obtained by the present study. A vibrator similar to that employed by Hunt and McIntyre was used in the present experiments, but the drive was provided by a pulse generator. Perhaps the more ra-

pid coil movement produced by the rectangular wave input to the vibrator activated the "hair" units more effectively than would have been possible with a sinusoidal drive. It is also clear from the present experiments that "hair" units will follow repetitive puffs of air for many seconds at frequencies of 220-230/sec., the highest that could be obtained with the apparatus available. Yamamoto, Sugihara, and Kuru (1958) have found that "hair" units are present in the dorsal columns at the upper cervical level, and their results resembled those obtained in the present study in showing that "hair" units located distally on the extremities tend to have smaller receptive fields than units located more proximally. It would appear therefore that "hair" units similar to those described in peripheral nerves and dorsal roots are present in the dorsal columns. The present experiments have served to define somewhat more precisely certain of the properties of dorsal column "hair" units. Whether units with these properties also constitute part of the input to lateral funicular units is not known.

#### B. Tonic touch units

Adrian and Zotterman in 1926 described slowly adapting receptors in the pad skin of the cat, and noted that they showed velocity sensitivity. It is likely that these units are similar to the tonic pad units studied in the present experiments, and apparently no later studies have been made of these units. Tonic units in the hairy skin of the rabbit were described by Frankenhauser (1949). More recently, Witt and Hensel (1959) recording from cat peripheral nerves, and Hunt and McIntyre (1960b) recording from cat dorsal roots, have studied these units in some detail, noting that they show responses to thermal stimuli and are readily inactivated by strong mechanical stimulation. In fact, Witt and Hensel (1959) described several different types of cutaneous receptors which could be influenced by both mechanical and thermal stimuli. These receptors were apparently all slowly adapting to mechanical stimulation, and all showed a transient increase in activity during cooling and a transient decrease in activity during warming. A few of the receptors showed spontaneous and evoked activity which was quite regular, in contrast to the units studied in the present experiments. Only one type of unit, that which they found most commonly in their material, seems to correspond to the tonic dorsal column units studied in these experiments. These particular units showed no spontaneous activity, were transiently activated by cooling, transiently inhibited by heating, and showed increased levels of excitability at steadily elevated temperatures.

Witt and Hensel noted that the discharge in these units to maintained mechanical stimulation was irregular, and this apparently also was true of the discharge to cooling, though the authors make no specific comment on this point. In this latter respect the results of Witt and Hensel depart from those obtained in the present experiments, though it is not clear that they made a systematic study of the response of these units to cooling. Hunt and McIntyre also did not comment on the occurrence of a more regular discharge in tonic units during cooling. Iggo (1963), recording from peripheral nerves in the cat, has studied tonic cutaneous units with receptor structures in hairy skin. He has demonstrated that these receptors are associated with small dome-like elevations on the skin of the animal, and that they possess a characteristic morphology. The properties of these units seem to be similar to those studied in the present experiments, an irregular discharge being characteristic of the response to maintained mechanical deformation, although it was not determined whether the tonic units studied in the present experiments were associated with elevations on the skin. Iggo noted that these units respond transiently to cooling, and emphasized the fact that the maximum frequency of discharge that could be obtained in response to cooling (50/sec.) was less than one tenth that which could be obtained with appropriate high velocity mechanical stimulation (800-1000/sec.). No mention is made of any increase in the regularity of the discharge during cooling, and in the single cooling response illustrated there is no indication of regularity. The reason for the difference between these results and those obtained in the present experiments is not clear. There are indications that the rate of cooling is important, more rapid cooling tending to produce more regular activity; and, as has already been stressed, cooling through a low temperature range seems important in producing a regular response. It can only be said that in the present study a regular response has been seen in all cases when cooling occurred through the appropriate range of temperatures.

It is interesting to note that primates, including man, have been found to possess rapidly adapting "hair" type receptors, as well as large fiber slowly adapting mechano-sensitive receptors similar to those described in the cat (Hensel and Bowman 1960, Iggo 1963b).

#### C. Phasic pad units

Phasic pad units have been studied by Armett and Hunsperger (1961), recording from peripheral nerve or dorsal root fibers in the cat, and Armett et al. (1961, 1962) have recorded post synaptic activity in the dorsal horn of the

cat spinal cord initiated by units of this type. These investigators have made no attempt to determine whether these units respond to thermal stimuli and have largely confined themselves to activating the units with very short mechanical pulses producing only a single nerve impulse. The units have receptive fields that were rather large, similar to those found in the present experiments, and were in almost all cases confined to the main foot pad. In the present study no receptive fields were found outside the main pad. Thus it would be anticipated that the receptor structures associated with phasic pad units would be found only in the main pad and not in the smaller toe pads. The ability of these units to follow high frequency repetitive stimulation suggests that they might be Paccinian corpuscles (Hunt 1961), which are known to be present in the skin of the cat's main pad (Winkelmann 1958).

## II. Inactivation

In his early studies of pain, Adrian (1931) noted that stimuli which damaged the skin tended to inactivate large fiber low threshold mechanoreceptors. Lindblom (1958) found that strong pressure inactivated rapidly adapting low threshold mechanoreceptors in the skin of the frog, and Hensel and Zotterman (1951) made similar observations while studying mechanoreceptors in the cat's tongue. A systematic study of these effects was undertaken by Feng (1933), who produced inactivation of cutaneous mechanoreceptors in both the frog and the cat by scraping the skin. He found that if the scraped area was flushed with saline, activity in the mechanoreceptors was restored, and presented evidence that potassium liberated from damaged tissues had caused the inactivation. Thus in view of these earlier studies, the finding in the present experiments that dorsal column units are inactivated by damaging stimuli is not unexpected. Such findings do emphasize the fact that there must be appreciable differences between the afferents which signal mechanical events and those which signal pain, because the latter are activated and sensitized in just those situations where the former are inactivated.

## III. Lateral Column Units

### A. Type I Units

Type I Units have been studied by Wall (1960) and by Wall and Cronley-Dillon (1960). The results obtained by these investigators agree in most but not all respects with those obtained in the present experiments. There is agreement that these units can be very effectively driven by gentle mechanical stimuli, and that they discharge in a maintained fashion in response to maintained

mechanical stimulation. The occurrence of a bursting after-discharge following "noxious" mechanical stimulation was also described, as was the response to heating. Results differ concerning the frequency of the maintained discharge in response to strong mechanical stimulation, compared with the frequency in response to moderate mechanical stimulation. In the present experiments, the usual finding was that no increase in frequency occurred when the pressure was increased from "firm" to "noxious", with some cases in which an increase did occur, and others in which there was a decrease in frequency. Wall describes only an increase in frequency as mechanical stimulation becomes stronger. Another difference concerns the temperature at which the response to heating the skin begins. According to Wall there is a response when the temperature is elevated 3 to 4°C above neutral skin temperatures. In the present experiments an appreciable response occurred only after the skin temperature reached 44 or 45°C. A possible reason for this difference might be that Wall estimated the temperature changes with a subcutaneous thermistor, while in the present experiments skin surface temperature was measured. With the former method it is possible that the temperature of the receptors might be considerably higher than the temperatures of the thermistor, especially if the temperature was elevated rapidly. Wall does not indicate the rate at which the temperature was altered in his experiments.

The nature of the peripheral fibers which constitute the input to type I units is a matter of conjecture. It is clear that at least some of these fibers differ in certain respects from those which enter the dorsal columns, because receptors which activate type I units when the skin is stimulated mechanically are resistant to inactivation by strong thermal and strong mechanical stimuli, and respond well when stimulated with a smooth object. Also there is the observation that type I units often showed after discharge following mechanical stimulation, whereas dorsal column units never showed this type of response. It is not known whether the after discharge in type I units is a reflection of after discharge in the afferent fibers which excite these units, or whether it originates in the spinal cord itself, but is interesting to note that both small myelinated (Zotterman 1939) and unmyelinated (Zotterman 1939, Iggo 1960) fibers have been reported to produce an after discharge following mechanical stimulation. It is more difficult to account for the resistance of type I units to inactivation on the basis of the known properties of primary afferents, since Iggo (1960) has reported that mechanosensitive C fibers are readily depressed by repeated rubbing of the skin. In the present experiments no obvious depression

has been seen following such a procedure. Apparently no peripheral fibers of any size with an appreciable response to mechanical stimulation have been described in the mammal which are not depressed or inactivated by some form of vigorous mechanical or thermal stimulation. The responses of peripheral nerve fibers to stimulators of different texture does not seem to have been studied.

The activation of type I units by strong heating can be more readily explained on the basis of the known properties of primary afferents. Both Iggo (1959) and Iriuchijima and Zotterman (1960, 1961) have described C fibers which are activated by strong heating, and Witt and Hensel (1959) found such activity to be quite prominent among the small myelinated fibers in their material. It is not certain that any of these fibers are actually able to evoke activity in type I units, but the temperature at which increased activity begins is similar in both peripheral fibers and type I units.

Wall and Cronly-Dillon have suggested that type I units might be part of a pain pathway. Since it is clear that these units can be very effectively driven by gentle mechanical stimulation, pain sensations were considered by these investigators not to be related to the overall frequency of discharge in these units, but rather to be linked with some particular pattern of activity. The nature of this pain pattern was not defined. In the present experiments, it was not possible to demonstrate any characteristic pattern of discharge in single type I units when damaging stimuli were applied. It is possible however that some alteration in the overall pattern of activity in a number of type I units might occur when stimuli become noxious, with the result that pain is felt. It will be necessary to record from many more type I units before this possibility can be properly evaluated. Kolmodin and Skoglund (1960) have described units in the gray matter of dorsal horn of the spinal cord which respond specifically to noxious mechanical stimuli. Wall in his studies of this region has not reported units which respond in this fashion and none have been found in the white matter of the spinal cord during the present experiments. If confirmed, the findings of Kolmodin and Skoglund might be of considerable interest in relation to spinal systems mediating pain.

#### B. Type II Units

The responses of Type II units to cutaneous stimuli do not seem to have been studied in detail by previous investigators. The present experiments have indicated that they differ from type I units in their pattern of discharge in receptive

field organization, and in not being well driven by gentle mechanical stimulation. There seems to be a general tendency for units located more ventrally in the lateral funiculus to be less readily activated by gentle mechanical stimuli than the more dorsally located type I units. It is interesting that strong to moderate mechanical stimuli are required to activate motoneurons (Talbot 1964), which are ventrally located in the gray matter of the spinal cord. It would appear that activity elicited by gentle mechanical stimulation is in some way excluded from the more ventrally located cells and fibers which have been studied thus far. Therefore, these more ventral units show responses to a more restricted range of stimuli than do the dorsally situated type I units. The comments made concerning the nature of the peripheral nerve fibers eliciting activity in type I units apply equally to type II units.

#### IV. Studies at Higher Levels

A number of investigations have been made of single cells in the thalamus and cortex responding to cutaneous stimuli. In all but a few cases only mechanical stimuli have been employed, and as a result the studies have little bearing on the problem of modality discrimination. However, Landgren (1957a, 1957b, 1960a, 1960b) has tested the response range of single cells activated from the tongue in both the thalamus and cortex of the cat. This would seem to be an especially favorable cell population for study in as much as considerable information is available from the investigations of Zotterman and co-workers concerning the behavior of primary afferent fibers innervating the tongue. Landgren was concerned primarily with the question of whether particular thalamic or cortical cells would respond to more than one kind of cutaneous stimulation, and found that at the thalamic level almost all the cells studied responded either to moderate cooling or mechanical stimuli but not to both. Very few cells were found which responded to warming or taste stimuli. At the cortical level the situation was somewhat changed, and though the majority of cells responded only to mechanical stimulation, more cells responded to both cooling and mechanical stimulation than to cooling alone. There is no obvious explanation for this apparent increase in convergence at the cortical level. It would be interesting to know whether the pattern of activity in response to cooling was the same as in response to mechanical stimulation in these polymodal cells. It is nevertheless significant that units have been found in both the thalamus and cortex which respond in a specific fashion to different kinds of cutaneous stimulation.



Several single unit studies at the thalamic level have been concerned with the problem of locating cells which respond specifically to noxious stimuli. These efforts have not met with conspicuous success, and there is considerable disagreement among different investigators concerning the types of responses that can be found in the various thalamic nuclei. Poggio and Mountcastle (1960) have studied two adjacent thalamic areas which they found to show quite different properties. The more rostral of these is referred to as the ventrobasal complex (VB) and has been shown by anatomists (see Bowsher 1961) to receive an extensive projection from the dorsal column system. The more caudal region is called the posterior group (PO) and has been shown to receive both a dorsal column input (Bowsher 1961) and fibers from the lateral funiculus (Mehler, Feferman, and Nauta 1960). Poggio and Mountcastle found that single units in VB had small receptive fields and were well activated by gentle to moderate mechanical stimulation, properties similar to those seen in the dorsal columns during the present experiments. The units studied in PO responded in a quite different fashion. They were excited from large receptive fields which were often bilateral, and they were sometimes activated by auditory as well as mechanical stimuli. Frequently a particular unit could be activated by moderate mechanical stimulation applied to one area, but when another region was stimulated noxious pressure was required. However, over 50% of the units were excited exclusively by noxious mechanical stimulation. Whitlock and Perl (1961) and Perl and Whitlock (1961) have examined the responses of single thalamic neurons to both strong mechanical and strong thermal stimuli applied to cats and monkeys in which the dorsal columns had been cut. They agreed with Poggio and Mountcastle in finding cells in VB with small receptive fields which could be well activated by gentle or moderate mechanical stimulation. They described cells in the intralaminar region which could be activated only by noxious stimuli, as reported by Kruger and Albe-Fessard (1960) and Albe-Fessard and Kruger (1962). They were unable, however, to find any significant number of cells in PO which responded to noxious stimulation. This finding is in conflict with that of Poggio and Mountcastle and makes it difficult to evaluate whatever relationship PO might have to sensory systems mediating pain.

The observation that cells in the intralaminar region respond specifically to noxious stimuli is of considerable interest in view of the failure to locate significant numbers of such cells in any other part of the central nervous system.



The relationship of the intralaminar region to sensory systems mediating pain is unclear, however, because individual intralaminar cells can generally be excited from the entire surface of the body (Albe-Fessard and Kruger 1962), which would seem to render difficult any accurate localization of the site being stimulated, and because anatomical evidence (Powell and Cowan 1956, Mehler et. al. 1960) links the intralaminar nuclei with motor mechanisms.

It is evident that little clear information is available from single unit studies concerning those parts of the thalamus which might be involved in mediating pain. Other investigations in which gross potential recording has been used in conjunction with electrical stimulation of tooth pulp (Brookhart, Livingston, and Haugen 1953, Melzac and Haugen 1957, Melzac, Stottler and Livingston 1958) or electrical stimulation of peripheral C fibers (Collins and Randt 1956, 1958, 1960) have suggested that certain central brain stem structures could be involved in mediating pain. Further experiments employing single unit recording and natural stimuli are needed in order to evaluate these experiments. It should be particularly noted that C fibers can be activated by a range of natural stimuli, some of which are clearly non-noxious, and therefore a certain region of the nervous system can not be associated with pain sensory mechanisms on the basis of C fiber input alone.

#### V. Other Sensory Systems

In assessing the role of patterns in the transmission of sensory information, it is of interest to consider the gustatory system (see Erickson 1963). There is little evidence for highly specific taste fibers, most single units responding to many different test solutions. Individual fibers do, however, differ from one another in the relative magnitude of the responses they display to different taste stimuli, and many different fiber types can be distinguished on the basis of responses to a few standard solutions. It has been proposed that an animal recognizes different gustatory stimuli by an examination of activity in a number of taste fibers, and this suggestion is supported by behavioral evidence. Thus according to this view a spatial-temporal pattern of activity in a population of fibers constitutes the basis for taste discrimination. This mechanism does not seem improbable, accounting as it does for the great variety of taste sensations that are experienced, at least by man.

Different patterns of activity have been observed, as a function of changing stimuli, in single goldfish retinal ganglion cells (Wagner, MacNichol, and Wolbarsht 1960). The cells studied were of the "on-off" type when illuminated with white

light, that is, transient discharges occurred both when the light was turned on and when the light was turned off. By choosing stimuli of particular wave lengths it was possible to convert such an "on-off" cell into a pure "on" type, or a pure "off" type. Evidence was obtained that the receptors producing the on effects were different from those producing the off discharge, because they showed different spectral sensitivities and were found in different parts of the ganglion cell receptive field. Just what significance these findings may have for mechanisms of color vision is not clear, but they do represent an example of stimulus dependent temporal patterns in single sensory cells.

### Conclusion

Dorsal column units appear best suited for conveying information about mechanical events at the surface of the body, especially movement of the skin. Rapidly adapting receptors seem very specific in this regard, responding at highest frequencies to high velocity mechanical stimulation of moderate intensity, showing no response to heating or cooling, and being inactivated rather than activated by strong heating and strong mechanical stimulation. Slowly adapting dorsal column units resemble rapidly adapting units in being driven to highest frequencies by gentle or moderate high velocity mechanical stimulation, and in being inactivated by strong heating and strong mechanical stimuli. They differed from rapidly adapting units in showing a response to cooling. The discharge that occurred during cooling was typically considerably more regular than any slowly adapting discharge of comparable frequency occurring in response to mechanical stimulation, and it is possible that these units could convey information regarding cooling of the skin. This thermal information would be of a relatively crude sort, however, because rather rapid cooling is required to evoke a discharge in slowly adapting dorsal column units, and there is no maintained discharge in response to maintained lowered temperatures. Both slowly and rapidly adapting dorsal column units have shown capacities for texture discrimination, and the mechanical properties of the dorsal column system seem highly evolved. In general, the results of the present experiments support the usual concepts concerning the function of the dorsal column (Rose & Mountcastle 1959).

Single lateral column fibers have almost invariably been found to be activated by more than one kind of cutaneous stimulation. Gentle or moderate mechanical stimulation, strong heating, and rapid cooling have all been effective. Characteristic and reproducible patterns of activity which depend in some obvious way on the kind of stimulation employed have not been found in single fibers. The most striking differences in patterns of discharge observed in the lateral columns have been between different units, and have seemed to be characteristic of the unit and not of the type of stimulation used to activate it. Strong heating and strong mechanical stimuli have shown little tendency to depress activation of lateral column units by any of the stimuli effective in exciting them.

The present and other studies of primary afferent fibers have, for the most part, supported the notion that cutaneous receptors respond predominantly or exclusively to one kind of stimulation. An exception are the C fibers described

by Witt (1962) which can be equally well activated by mechanical stimulation, heating and cooling. Studies of peripheral nerve fibers have been conducted for the most part with reasonably careful control of the stimuli employed, and with the use of different kinds of stimulation while recording from individual units. In contrast, most of the investigations of sensory activity in the spinal cord and brain have been characterized by less vigorous control of the stimuli applied, and a tendency to use only one or very few different kinds of cutaneous stimulation. As a result less is known about the degree to which central neurons are specific with regard to the stimuli which activate them. The work of Landgren (1957a, 1957b, 1960a, 1960b) has shown that there are some cells at both the thalamic and cortical level which respond specifically to either moderate cooling or mechanical stimulation and other cells which respond to both moderate cooling and mechanical stimulation. These studies seem to be the only ones devoted to this problem at the more rostral levels of the nervous system. The findings of Landgren are of interest in view of the difficulties which have been experienced in locating cells in the trigeminal nucleus or spinal cord which respond to moderate thermal stimuli.

Units which respond specifically to noxious stimuli have been elusive at all levels of the nervous system. Only a few peripheral fibers can be shown to bear any convincing relationship to the mediation of pain, these being the C fibers which respond to strong thermal stimulation, described by Iggo (1959) and Iriuchijima and Zotterman (1960, 1961). No unambiguous data seems to be available associating any part of the trigeminal nucleus, thalamus or cortex with systems subserving pain. It is clear that the present experiments have not clarified the mechanisms whereby impulses giving rise to pain are transmitted at the spinal level. Various reasons for this failure are possible, but one that should be given serious consideration is the fact that the recording technique excludes small fibers. Light microscopic studies have shown that a great many of the myelinated fibers in the lateral funiculus are smaller than 3 or 4 microns in diameter (Häggqvist 1936, van Beusekom 1955), too small to be reached in any numbers with the electrodes employed in these experiments. Information concerning whether even smaller, unmyelinated fibers are present in the white matter of the spinal cord must await electron microscopic studies. In addition, it should be noted that not all parts of the white matter have been adequately studied in the present experiments. No recordings whatever have been made from the ventral funiculus, and the most ventral part of the lateral funiculus has not often been

penetrated.

In view of the difficulties involved in making a thorough analysis of the small cells and fibers in the spinal cord, it may be desirable to approach the problem of pain mediation at the spinal level by first determining more precisely through the use of spinal lesions those parts of the spinal cord which transmit pain. If this could be accomplished, then it would be possible to devote some considerable effort to recording from all the fibers in the region implicated.

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